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T R A N S L A T I O N

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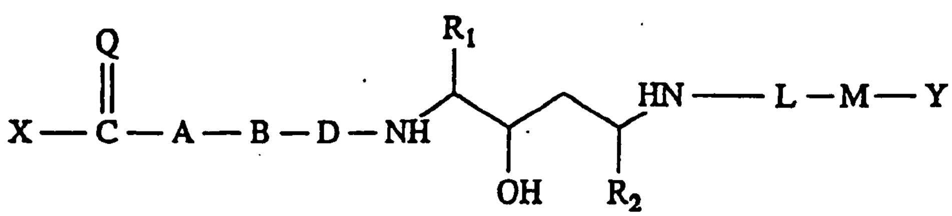
Title:

RETROISOSTERIC DIPEPTIDES, PROCESS FOR THEIR PRODUCTION AND THEIR USE AS RENIN INHIBITORS IN DRUGS

Summary

The invention concerns new retroisosteric dipeptides of general formula I



(I)

in which X, Q, A, B, D, L, M, Y, R_1 and R_2 have the meaning reported in the description, processes for their production and their use as renin inhibitors in drugs especially in circulation-influencing drugs.

Description

The invention concerns new retroisosteric dipeptides, processes for their production and their use as renin inhibitors in drugs, especially in circulation-influencing drugs.

Renin is a proteolytic enzyme which is produced predominantly by the kidneys and secreted into the plasma. It is known that renin in vivo splits off the decapeptide angiotensin I from angiotensinogen. Angiotensin I in turn is broken down in the lungs, the kidneys or other tissues into the octapeptide angiotensin II which has an effect on the blood pressure. The various effects of angiotensin II such as vasoconstriction, Na^+ retention in the kidneys, aldosterone liberation in the adrenals and tonus elevation of the sympathetic nervous system act synergistically in the sense of a blood pressure elevation.

The activity of the renin-angiotensin system can be manipulated by inhibiting the activity of renin or the angiotensin conversion enzyme (ACE) and by blockade of angiotensin II receptors pharmacologically. The development of orally applicable ACE inhibitors thus has led to new antihypertensives (cf. DOS 3628650, Am J. Med. 77, 690, 1984). ACE, however, also acts on other substrates than angiotensin I such as kinins. These may evoke undesirable side effects such as prostaglandin liberation and a series of behavioral and neurological effects. The ACE inhibitors also led to an accumulation of angiotensin I. A specific approach is to intervene at an early time in the renin-angiotensin cascade, i.e. by inhibition of the acid aspartase renin which recognizes only angiotensinogen as a substrate.

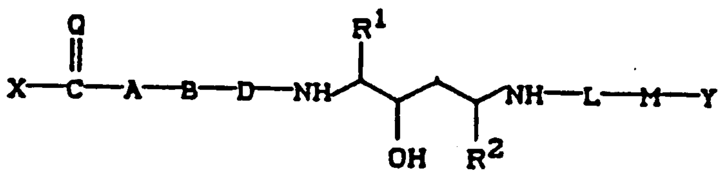
To date various types of renin inhibitors have been developed: renin specific antibodies, phospholipids, peptides with the N-terminal sequence of prorenin, synthetic peptides as substrate analogs and modified peptides. For

many renin inhibitors, the Leu-Val dipeptide is replaced by statin (EP 077029) or by isosteric dipeptides (cf. US 4424207).

In addition, in PCT WO 88/02374 renin inhibitors are claimed which contain retroisosteric dipeptide units as the protease-stable central part. Retroisosteric dipeptides have an amino group positioned at the head; the coupling to the C-terminal amino acids leads to a reversal of the amide function (retroamide) which is characterized by a high metabolic stability with respect to enzymatic breakdown.

Through the process according to the invention, new renin inhibitors have been found which surprisingly have high selectivity with respect to human renin and good oral efficacy.

The invention concerns retroisosteric acylated dipeptides of general formula (I)

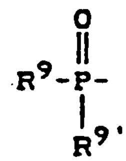


(I)

in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula

$$W\text{-}(CH_2)_n\text{-}\underset{}{\overset{\displaystyle R^3}{\overset{|}{C}}}H\text{-}\quad,\qquad R^4\text{-}NH\text{-}\quad,\qquad R^5R^6N\text{-}\overset{\displaystyle R^{3'}}{\overset{|}{C}}H\text{-}CH_2\text{-}$$

or for T, where R^3 and $R^{3'}$ are the same or different and signify straight chained or branched alkyl with up to 8 carbons atoms which is possibly substituted by aryl with 6 to 10 carbons atoms, n signifies the number 1, 2, 3 or 4, W is a group of the formula $R^7\text{-}CO\text{-}$, $R^8\text{-}SO_2\text{-}$ or



where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 8 carbons atoms or a 6-membered heterocycle with up to 3 heteroatoms from the series nitrogen, oxygen or sulfur,

R^9 and $R^{9'}$ are the same or different and denote hydroxy or alkoxy with up to 8 carbons atoms,

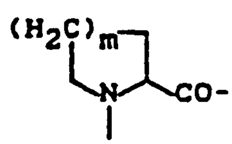
R^4 is a carbohydrate radical with 4 to 8 carbons atoms, the OH functions of the sugar possibly being shielded,

Q signifies oxygen or sulfur,

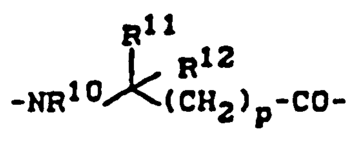
R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 8 carbons atoms, phenyl or an amino protective group,

T is a straight chained or branched alkenyl with up to 8 carbon atoms which is possibly substituted by aryl with 6 to 10 carbon atoms which in turn may be substituted by halogen, hydroxy or alkoxy with up to 6 carbon atoms,

A, B, and D are the same or different and stand for a direct bond or for a radical of the formula:



where m signifies the number 1 or 2 or stands for a group of the formula



where p signifies the number 0 or 1,

R^{10} denotes hydrogen, straight chained or branched alkyl with up to 6 carbon atoms or an amino protective group,

R^{11} and R^{12} are the same or different and denote: hydrogen or cycloalkyl with 3 to 8 carbon atoms, or a 3 to 8 membered heterocycle with up to 4 heteroatoms from the series of nitrogen, oxygen or sulfur, a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by alkylthio with up to 6 carbon atoms, hydroxy, mercapto, guanidyl or by a group of the formula $-NR^5R^6$ or R^{13}-OC, where R^5 and R^6 have the above-reported meaning, and R^{13} denotes a hydroxy, benzyloxy, alkoxy with up 6 carbon atoms or the above-listed group $-NR^5R^6$ or which is possibly substituted by aryl with 6 to 10 carbon atoms which in turn may be substituted by hydroxy, halogen, nitro, alkoxy with up to 8 carbon atoms or by the group $-NR^5R^6$, where R^5 and R^6 have the above-given meaning or which may possibly be substituted by a 5 or 6 membered nitrogen-containing heterocycle or indolyl, where the corresponding -NH- functions may possibly be shielded by alkyl with up to 6 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula

$$-CO-(CH_2)_{p'}-\overset{R^{11'}}{\underset{}{C}}(R^{12'})-NR^{10'}-$$

where p', $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the above-reported meaning for p, R^{10}, R^{11} and R^{12}, in their D or L form or as a D,L isomer mixture, R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms, Y stands for a group of the formula

$$-\overset{\displaystyle Q}{\overset{\|}{C}}-NH-R^4$$

or for $-CO-R^{14}$, where Q and R^4 have the above-reported meaning, R^{14} is a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by pyridyl, phenyl or the group $-NR^{15}R^{16}$ where R^{15} and R^{16} either have the above-reported meaning of R^5 and R^6 and are the same as or different from these, or R^{15} denotes hydrogen and R^{16} the group of the formula

$$-CO-\overset{\displaystyle R^3}{\overset{|}{C}H}-(CH_2)_n-W \quad \text{or} \quad -\overset{\displaystyle Q}{\overset{\|}{C}}-\underset{\displaystyle H}{N}-R^4$$

where W, Q, n, R^3 and R^4 have the above reported meaning, and their physiologically unobjectionable salts, with the qualification that X may signify tert-butoxy only when Y stands for the group

$$-\overset{\displaystyle Q}{\overset{\|}{C}}-NH-R^4 \quad \text{or}$$

The usual protective group such as methylbenzoyl, benzoyl, acetyl or benzyl are suitable as OH protective groups. Benzyl or acetyl are preferred. Acetyl (Ac) is especially preferred.

Amino protective group within the limits of the invention stands for the usual amino protective groups used in peptide chemistry.

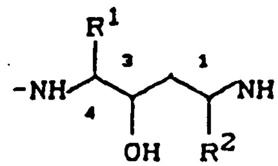
These include preferably: benzoyloxycarbonyl, 4-bromobenzyl-oxycarbonyl, 2-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 3,5-dimethoxybenzyl-oxycarbonyl, 4-methoxybenzyoxycarbonyl, 4-nitro-benzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxy-benzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, ethoxy-carbonyl, propoxycarbonyl,

isopropoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, isopentaoxycarbonyl, cyclohexoxycarbonyl, 2-chloroethoxycarbonyl, 2,2,2-trichlorethoxycarbonyl, 2,2,2-trichlor-tert-butoxycarbonyl, benzhydryloxycarbonyl, bis-(4-methoxyphenyl)-methoxycarbonyl, phenacyloxycarbonyl, 2-trimethylsilyl-ethoxy-carbonyl, 2-triphenylsilylethoxycarbonyl, methyloxycarbonyl, vinyl-oxycarbonyl, allyloxycarbonyl, fluorenyl-9 -methoxycarbonyl, ethyl-thiocarbonyl, methylthiocarbonyl, bintylthiocarbonyl, tert-butyl thiocarbonyl, benzylthiocarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2-iodoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl, 4-nitrobenzyl, 4-nitrobenzoyl, naphthylcarbonyl, phenoxyacetyl, adamantylcarbonyl, dicyclohexylphoshoryl, diphenyl-phosphoryl, dibenzylphophoryl, di-(4-nitrobenzyl)phosphoryl, phenoxyphenylphosphoryl, diethylphosphinyl, diphenylphosphinyl, or phthaloyl.

Especially preferred amino protective groups are benzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 4-methoxybenzyl-oxycarbonyl, 4-nitrobenzyl-oxycarbonyl, 2-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, cyclohexoxycarbonyl, 2-chloroethoxycarbonyl, phenoxyacetyl, naphthylcarbonyl, adamantyl-carbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, menthyloxycarbonyl, vinyloxy-carbonyl, allyloxycarbonyl, fluorenyl-9-methoxycarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, isovaleroyl or benzyloxymethyl.

The compounds according to the invention of general formula (I) have several asymmetrical carbon atoms. They may exist in the D or of the L form independently of one another. The invention includes the optic antipodes as well as the isomer mixtures or racemates. The groups A, B, D, L and M independently of one another exist in the optically pure, preferably in the L form.

The group of the formula



has 3 asymmetrical carbon atoms (1,3,4) which, independently from one another, may exist in the R or S configuration. This group preferably exists in the 1R, 3S, 4S configuration, 1R, 3R, 4S configuration, 1S, 3R, 4S configuration or in 1S, 3S, 4S configuration.

Especially preferred are the 1S, 3S, 4S configuration and the 1R, 3S, 4S configuration which reflect the configuration of an L,L dipeptide, depending on the nature of the substituent R^2.

The compounds of general formula (I) according to the invention may exist in the form of their salts. These may be the salts of the compounds according to the invention with inorganic or organic acids or bases. The acid addition products include preferably salts with hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid or carboxylic acids such as acetic acid, propionic acid, oxalic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, adipic acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, lactic

acid, ascorbic acid, salicylic acid, 2-acetoxybenzoic acid, nicotinic acid, isonicotinic acid, or sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, and naphthalene-sulfonic acids.

To be preferred are compounds of general formula (I) in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula:

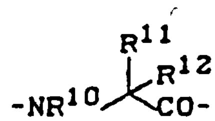
$$W\text{-}(CH_2)_n\text{-}\overset{\displaystyle R^3 \atop |}{C}H\text{-} \quad , \qquad R^4\text{-}\underset{\displaystyle H}{N}\text{-} \quad , \qquad R^5R^6N\text{-}\overset{\displaystyle R^{3'} \atop |}{C}H\text{-}CH_2\text{-}$$

or for T, where R^3 and $R^{3'}$ are the same or different and signify a straight chained or branched alkyl with up to 6 carbon atoms which may possibly be substituted by phenyl or naphthyl, n is a number 1, 2, or 3, W is a group of the formula R^7-CO-, R^8-SO_2- or

$$R^9\text{-}\overset{\displaystyle O \atop \|}{\underset{\displaystyle | \atop R^{9'}}{P}}\text{-}$$

where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 6 carbon atoms or morpholino, R^9 and $R^{9'}$ are the same or different and signify hydroxy or alkoxy with up to 6 carbon atoms, R^4 signifies a pyranosyl radical, where the OH function of the sugar may possibly be protected, Q denotes oxygen or sulfur, R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 6 carbon atoms or an amino protective group, T is a straight chained or branched alkenyl with up to 6 carbon atoms which is possibly substituted by phenyl which in turn may be substituted by fluorine, chlorine, hydroxy or alkoxy with

up to 4 carbon atoms, A, B and D are the same or different and stand for: - a direct bond, or - for proline, or - for a group of the formula



where R^{10} denotes hydrogen or a straight chained or branched alkyl with up to 4 carbon atoms, R^{11} and R^{12} are the same or different and denote cyclopentyl, cyclohexyl, hydrogen or straight chained or branched alkyl with up to 6 carbon atoms which may possibly be substituted by naphthyl or phenyl, which in turn may be substituted by fluorine, chlorine, nitro or alkoxy with up to 6 carbon atoms, or is substituted by indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, where the corresponding -NH functions may possibly be substituted by alkyl with up to 4 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula

where $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the above-reported meaning for R^{10}, R^{11} and R^{12} and are the same as or different from these, in their D or L form or as a D,L isomer mixture, R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl, Y for a group of the formula

$$-\overset{\displaystyle O}{\overset{\|}{C}}-NH-R^4$$

or stands for -CO-R^{14}, where Q and R^4 have the above-reported meaning, R^{14} is a straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by pyridyl, phenyl or by the group -$NR^{15}R^{16}$, where R^{15} and R^{16} are either the same or different and which have the above-given meaning of R^5 and R^6 and are the same as or different from these or R^{15} signifies hydrogen and R^{16} a group of the formula -

$$\begin{array}{l} R^3 \\ | \\ -CO-CH-(CH_2)_n-W \end{array}$$

or

$$\begin{array}{l} Q \\ \| \\ -C-NH-R^4 \end{array}$$

where W, Q, n, R^3 and R^4 have the above-given meaning, and their physiologically unobjectionable salts with the qualification that X may signify tert-butoxy only if Y stands for the group

$$\begin{array}{l} Q \\ \| \\ -C-NH-R^4 \end{array}$$

or

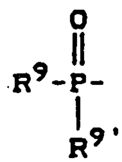
especially preferred are compounds of general formula (I) in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula

$$\begin{array}{l} R^3 \\ | \\ W-(CH_2)_n-CH- , \end{array}$$

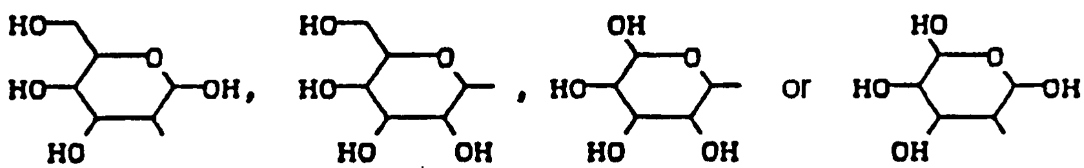
R^4-NH-,

$$\begin{array}{l} R^{3'} \\ | \\ R^5R^6-N-CH-CH_2- \end{array}$$

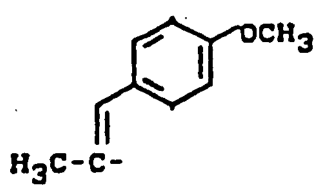
or for T, where R^3 and $R^{3'}$ are the same or different and denote straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by phenyl or naphthyl, n is a number 1 or 2, W is a group of the formula R^7-CO- R^8-SO_2- or



where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 4 carbon atoms or morpholino, R^9 and $R^{9'}$ are the same or different and denote hydroxy or alkoxy with up to 4 carbon atoms, R^4 is a radical of the formula



where the OH functions are possibly protected by acetyl, Q signifies oxygen or sulfur, R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 4 carbon atoms or an amino protective group, T denotes the radical of the formula



A, B and D are the same or different and stand for: a direct bond, or for proline, or for a group of the formula

where R^{10} denotes hydrogen or methyl, R^{11} and R^{12} are the same or different and signify cyclopentyl or straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by naphthyl or phenyl which in turn may be substituted by fluorine, chlorine, or alkoxy with up to 4 carbon atoms, or alkyl is substituted by imidazolyl, triazolyl, pyridyl or pyrazolyl, where the -NH functions are possibly protected by methyl, Boc or BOM, L and M are the same or different and stand for a direct bond or for a group of the formula

where $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the meaning reported above for R^{10}, R^{11} and R^{12} and are the same as or different from these, in their D or L form or as a D,L isomer mixture,

R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 4 carbon atoms possibly substituted by cyclohexyl or phenyl,

Y stands for a group of the formula

$$-\overset{\overset{\displaystyle Q}{\|}}{C}-NH-R^4$$

or for $-CO-R^{14}$, where Q and R^4 have the above-given meaning,

R^{14} is a straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by pyridyl, phenyl or by the group $-NR^{15}R^{16}$ in which R^{15} signifies hydrogen and R^{16} a group of the formula

$$-\mathrm{CO}-\overset{\displaystyle R^3 \atop |}{\mathrm{CH}}-(\mathrm{CH_2})_n-\mathrm{W}$$

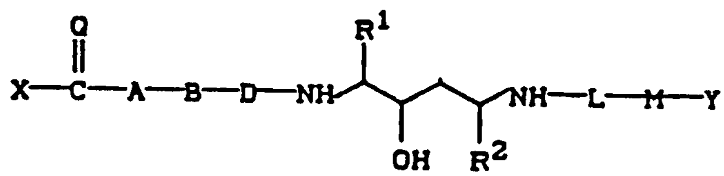
or

$$-\overset{\displaystyle Q \atop \|}{\mathrm{C}}-\mathrm{NH}-R^4$$

where W, Q, n, R^3 and R^4 have the above-reported meaning, and their physiologically unobjectionable salts with the qualification that X may signify tert-butoxy only when Y stands for the group

$$-\overset{\displaystyle Q \atop \|}{\mathrm{C}}-\mathrm{NH}-R^4 \quad \text{or}$$ 

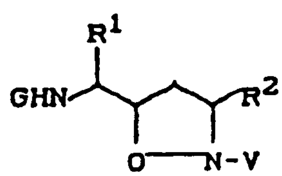
In addition a process was found for the production of compounds according to the invention of general formula (I)



(I)

in which X, A, B, D, R^1, R^2, L, M, Q and Y have the meanings given above, characterized by the fact that:

compounds of general formula (II)

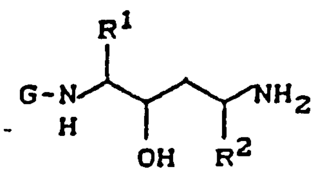


(II)

in which R^1 and R^2 have the above-given meaning,

G stands for one of the above-listed amino protective groups and

V stands for a radical capable of being split off hydrogenolytically, e.g. benzyl, are first reduced by hydrogenolysis with opening of the isoxazolidine ring into the amino alcohols of general formula (III)



(III)

where G, R^1 and R^2 have the above-reported meaning, and then possibly condensed with compounds of general formula (IV) or (IVa)

$$HO—L'—M'—Y \quad (IV) \qquad HO-Y \quad (IVa)$$

in which Y has the above-given meaning, and

L' and M' have the above given meaning for L and M but not simultaneously standing for a direct bond, in inert solvents, if necessary in the presence of a water-removing accessory material and/or a base, and then after splitting off of protective G by conventional methods are reacted with compounds of general formula (V)

$$G'—B'—D'—OH \quad (V)$$

in B' and D' have the above-given meanings of B and D but do not stand simultaneously for a direct bond, and

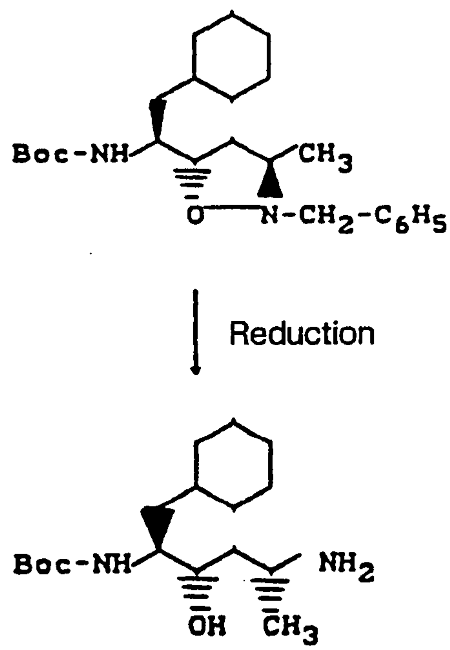
G' has the above given meaning for G and is the same as or different from it, and in a last step after the splitting off of the protective group G', are reacted with compounds of formula (VI)

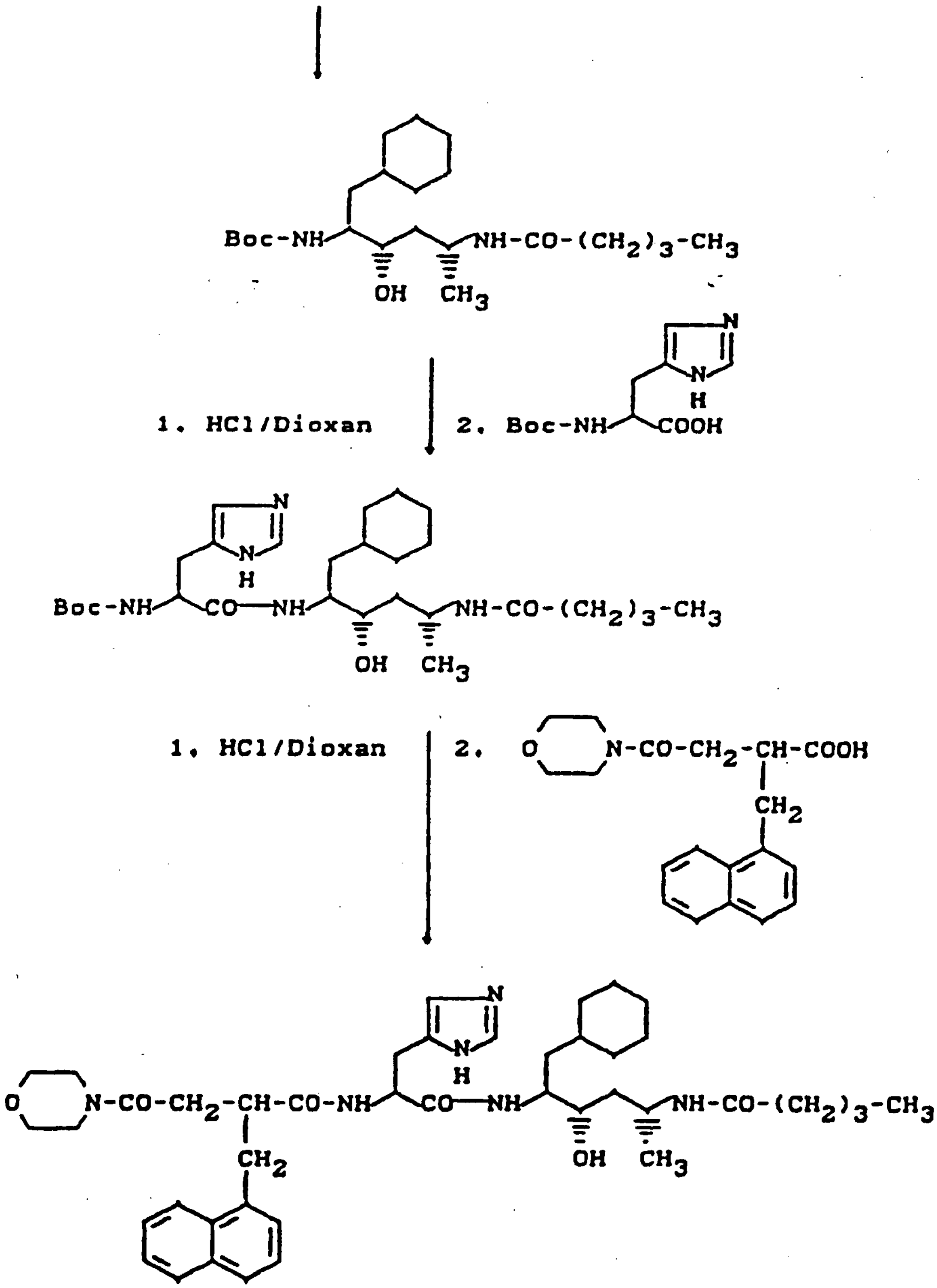
$$X-\overset{\overset{\displaystyle Q}{\|}}{C}-A'-OH \quad (VI)$$

in which X and Q have the above given meaning, and

A' has the meaning given above for A but does not stand for a direct bond, if necessary in the presence of a base.

The process according to the invention can be illustrated by the following formula diagram by way of example:




Boc-NH
OH
CH3
NH-CO-(CH2)3-CH3
1. HCl/Dioxan
2. Boc-NH
COOH
1. HCl/Dioxan
2.
N-CO-CH2-CH-COOH
CH2
N-CO-CH2-CH-CO-NH
CO
NH

As solvents, the conventional inert solvents which do not change under reaction conditions are suitable for all process steps. Here belong preferably organic solvents such as methanol, ethanol, propanol, isopropanol or ethers such as diethyl ether, glycol monomethyl or dimethyl ether, dioxane or tetrahydrofurane or [hydro]carbons such as benzene, toluene, xylene, cyclohexane or petroleum fractions, or halohydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, or acetone, dimethylsulfoxide, dimethylformamide, hexamethylphosphoric acid triamide, acetic ester, pyridine, triethylamine or picoline. It is also possible to use mixtures of the above named solvents.

Especially preferred for the reduction are methanol and acetic acid ethyl ester, for the peptide coupling and the reaction with compounds of general formula (IV), (IVa) and (VI) methylene chloride.

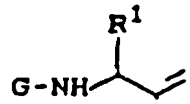
The reduction of the compounds of general formula (II) takes place either with the usual catalysts such palladium hydroxide or palladium/carbon, preferably with palladium/carbon or via a catalytic transfer hydrogenation in the usual manner (cf. Tetrahedron 41, 3469 (1985), 3463 (1985), Synthesis 1987 531.

The catalyst is used in a quantity of 0.05 to 1.0 moles, preferably 0.1 to 0.5 mole relative to 1 mole of the compound of general formula (II).

The reduction is conducted in the temperature range from 40 to 160°C, preferably from 60 to 80°C.

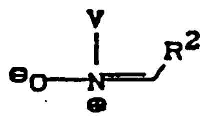
The reduction can be conducted both at standard pressure and also at elevated or reduced pressure (e.g. 0.5 to 5 bar), preferably at standard pressure.

The compounds of general formula (II) are new and can be synthesized by reacting compounds of general formula (VII)



(VII)

in which G has the above-given meaning, in a cycloaddition reaction with compounds of general formula (VIII)



(VIII)

in which V and R^2 have the above-given meaning, if necessary in the presence of inert organic solvents.

Suitable solvents are the conventional organic solvents which do not change under the reaction conditions. These include preferably alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol or ethers such as diethyl ether, dioxane, tetrahydrofurane, glycol monoethyl or diethyl ether or hydrocarbons such as benzene, toluene, xylene or petroleum fractions or acetic acid n-butyl ester. Preferred are n-butanol, dioxane, acetic-n-butyl ester, toluene, xylene or mesitylene.

The reaction can be in a temperature range from 0 to 250°C, preferably at 100-170°C at standard or elevated pressure.

The compounds of general formula (VII) are well known or can be synthesized by ordinary methods [Chem. Pharm. Bull 30, 1921 (1982), Chem. Pharm. Bull. 23, 3106 (1975, J. Org. Chem. 47, 3016 (1982)].

The compounds of general formula (VIII) are well known or can be synthesized by conventional methods [J. J. Tufariello in 1,3-Dipolar

cycloaddition chemistry, vol. 2, ed. A. Padwa, p. 83-168, John Wiley (1984), R. Huisgen, H. Seidel, J. Bruning, Chem. Ber. 102, 1102 (1969)].

The compounds of general formula (III) are known in part [(R^1 = butyl, R^2 = propyl (I)), cf. PCT WO 88/02374] but may also be obtained by the above-reported new process via the step of isoxazolidine (formula II) in the preferred stereochemistry and in better yields.

The compound of general formulas (IV) and (V) are well known and can be produced by reacting a corresponding fragment consisting of one or more amino acid units with a free carboxyl group possibly existing in activated form with a complementary fragment consisting of one or more amino acid units, with an amino group, possibly in activated form, and by repeating this process with corresponding fragments, and then if necessary protective groups can be split off or replaced by other protective groups [cf. Houben Weyl, Methoden der organischen Chemie, Synthese von Peptiden II, 4 edition, vol. 15/1, 15/2, Georg. Thieme Verlag, Stuttgart].

As accessory materials for the peptide coupling and introduction of the radical Y (formulas (IV) and (IVa)) preferably condensation agents are used which may also be bases, especially if the carboxyl group is present in activated form as an anhydride. Here the usual condensation agents such carbodiimides are preferred, e.g. N,N'-diethyl, N,N'-dipropyl, N,N'-diisopropyl, N,N'-dicyclohexyl carbodiimide, N-(3-dimethylamino-isopropyl)-N'-ethylcarbodiimide hydrochloride, or carbonyl compounds such as carbonyl diimidazole or isoxazolium compounds such as 2-ethyl-5-phenyl-isoxazolium 3-sulfonate or 2-tert-butyl-5-methylisoxazolium perchlorate or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline or

propane-phosphonic acid anhydride or isobutyl chloroformate or benzotriazolyloxy-tri(dimethylamino)-phosphonium hexafluoro-phosphate.

As basis for peptide coupling and in the reaction with compounds of general formula (VI) one may use an alkali carbonate, e.g. sodium or potassium carbonate or hydrogen carbonate or organic bases such as trialkylamines, e.g. triethylamine, N-ethylmorpholine, N-methylpyridine or N-methylmorpholine. Triethylamine is preferred.

The accessory materials and bases are used in a quantity from 0.5 to 4 moles, preferably 1 to 1.5 mole relative in each case to 1 mole of the compounds of general formula (VI).

The peptide coupling is conducted in a temperature range from -20 to 100°C, preferably at 0 to 25°C and at standard pressure.

The radicals X and Y are introduced in a temperature range from 0 to +90°C, preferably at room temperature.

The reactions can be conducted both at standard pressure and also at elevated or reduced pressure (e.g. 0.5 to 5 bar), preferably at standard pressure.

The compounds of general formulas (IVa) and (VI) are well known or can be synthesized by conventional methods.

The splitting off of the protective groups in each case before the individual peptide couplings takes place in the usual way under acid or basic conditions or reductively by catalytic hydrogenation, e.g. with Pd/C inorganic solvents such as ethers, e.g. tetrahydrofuran or dioxane or alcohols such as methanol, ethanol or isopropanol [cf. Protective Groups in Organic Synthesis, W. Greene, John Wiley and Sons, New York, 1981; Chemistry and Biochemistery of the Amino Acids, G. C. Barrett, Chapman and Hall, London, New York 1985].

In vitro test

The inhibitory strength of the peptides according to the invention against endogenous renin from human plasma is determined in vitro. Pooled human plasma is obtained by the addition of ethylenediamine tetraacetic acid (EDTA) as an anticoagulant and stored at -20°C. The plasma renin activity (PRA) is determined as the rate of formation of angiotensin I from endogenous angiotensinogen and renin after incubation at 37°C. The reaction solution contains 150 µl of plasma, 3 µl of 6.6% 8-hydroxyquinoline sulfate solution, 3 µl of 10% dimercaprol solution and 144 µl of sodium phosphate buffer (0.2 M, 0.1% EDTA, pH 5.6) with or without the materials according to the invention in various concentrations. The angiotensin I formed per unit time is determined by a radioimmunoassay (Sorin, Biomedica, Italy). The percentage inhibition of the plasma renin activity is calculated by comparison of the substances claimed here. The concentration range in which the substances claimed here display a 50% inhibition of plasma renin activity is between 10^{-4} and 10^{-9} M.

The standard concentration used of the following renin inhibitors is 50 µg/ml. At more than 90% inhibition the IC_{50} values are determined.

Example No.	in vitro 50 µm/ml (%)	IC_{50} (M)
1	100%	2.0×10^{-9}
2	100%	1.3×10^{-9}
7	100%	7.4×10^{-7}

The new active principles can be transformed into the conventional formulations by the usual methods such as tablets, coated pills, granulates, aerosols, syrups, emulsions, suspensions and solutions by using inert, nontoxic pharmaceutically suitable vehicles or solvents. In this case the therapeutically effective compound in each case should be present in a

concentration of about 0.5 to 90 wt. % of the total mixture, i.e. in quantities sufficient to achieve the reported dosage range.

The formulations are produced, for example, by diluting the active principles with solvents and/or carrier materials, if necessary using emulsifiers and/or dispersing agents, in which case, if water is used as the diluting agent, organic solvents may, if necessary, be used as accessory solvents.

Examples of accessory materials include:

Water, nontoxic organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. peanut/sesame oil), alcohols (e.g. ethyl alcohol, glycerine), vehicles such as natural stone meals (e.g. kaolins, aluminas, talcum, chalk), synthetic stone meals (e.g. finely dispersed silicic acid, silicates), sugar (e.g. cane, milk and grape sugar), emulsifiers (e.g. polyoxyethylene fatty acids esters), polyoxyethylene fatty alcohol ethers (e.g. lignin, sulfite waste liquors, methyl cellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talcum, stearic acid and sodium lauryl sulfate).

They are administered in conventional ways, preferably orally or parenterally, especially perlingually or intravenously. In the case of oral application, the tablets may naturally contain, besides the above mentioned vehicles, also additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch preferably potato starch, gelatine and the like. Also lubricants such as magnesium stearate, sodium lauryl sulfate and talcum may be used for the tableting. In the aqueous suspensions the active principles may be mixed, besides with the

above-mentioned accessory substances, also with various taste enhancers or dyes.

For the case of parenteral application, solutions of the active principles using suitable liquid carrier materials may be used.

Generally it has been found to be advantageous in the case of intravenous administration to administer quantities of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg body weight in order to achieve effective results, and in the case of oral application, this dosage is about 0.01 to 20 mg/kg, preferably about 0.1 to 10 mg/kg body weight.

Despite this it may occasionally be necessary to deviate from the quantities mentioned above, i.e. depending on body weight of the test animal or their nature of application but also because of the animal species and its individual behavior with respect to the drug or its nature, from its formulation and from the time or intervals in which the substance is administered.

Therefore in some cases it may be sufficient to get by with less than the above-named minimum quantity, while in other cases the above-mentioned upper limit must be exceeded. In the case of administration of larger quantities it may be recommended to distribute them in several individual doses over the day. For applications in human medicine the same dosage range is envisioned. The statements above also pertain here.

Appendix I

1. Amino acids

Generally the configuration is designated by prefixing an L or D to the amino acid abbreviation. In the case of the racemate, a D,L, where for

simplicity in the case of L-amino acids the configuration designation can be omitted and then an explicit designation is used only in the case of the D form or D,L mixture.

a) Natural amino acids

Ala	L-alamine
Asp	L-aspartic acid
Cys	L-cysteine
Gln	L-gluatamine
Glu	L-glutamic acid
His	L-histidine
Ile	L-isoleucine
Leu	L-leucine
Lys	L-lysine
Phe	phenylalanine
Cpg	cyclopentylglycerine
Val	Valine

2. Activation reagents and additives

HOBT	1-hydroxybenzothiazole
HOSU	N-hydroxysuccinimide
DCC	dicyclohexylcarbodiimide
NMM	N-methylmorpholine
BOP	benzothiazolyloxy-tris-(dimethylamino)-phosphonium hexafluorophosphate

3. Protective groups

BOC	tert-butoxycarbonyl
Z	benzyloxycarbonyl
AMP	2-aminomethylpyridiyl
BOM	benzyloxymethyl
PAA	pyridylacetyl

Appendix II

The following eluent systems were used:

A	ether:hexane	2:8
B	ether:hexane	3:7
C	ether:hexane	4:6
D	ether:hexane	7:3
E	$CH_2Cl_2:CH_3OH$	95:5
F	$CH_2Cl_2:CH_3OH$	98:2
G	$CH_2Cl_2:CH_3OH$	90:10
H	$CH_2Cl_2:CH_3OH:NH_3$	95:5:0.1
I	toluene:acetic ester	1:1
J	$CH_2Cl_2:CH_3OH:NH_3$	90:90:0.1

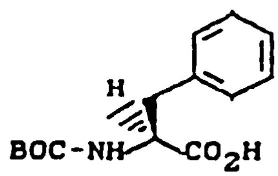
K	tol:acetic acid ethyl ester	25:75:1
L	nBuOH:HOAc:H_2O	8:2:2
M	tol:acetic acid ethyl ester	1:1
N	tol:acetic acid ethyl ester	1:3

For the compounds designated by x, ^{1}H-NMR data are available. The radical † listed in the examples stands for the tert-butyl group.

Initial compounds

Example 1.

BOC phenylalanine

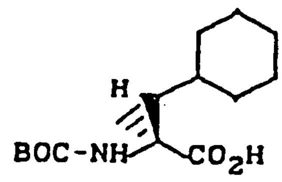


300 g (1.91 mole) of L-phenylalanine are suspended in 360 ml of dioxane and 360 of H_2O. 432.9 g (1.98 mole) of di-tert-butyl dicarbonate are added with stirring at pH 9.8. The pH is held constant with ca. 975 ml of 4 n NaOH. After 16 h the reaction mixture is extracted with ether, the aqueous phase is adjusted to pH 3-4 with citric acid and then extracted twice with ether and twice with acetic ester. The organic phases are combined and washed 3 times with water. After concentration and crystallization from diethyl ether/hexane one obtains 291.6 g (60.7%). m.p. 88-89°C.

NMR (DMSO, 300 MHz): δ = 1.35 (s, 9H, $C(CH_3)_3$).

Example II

BOC cylcohexylalanine

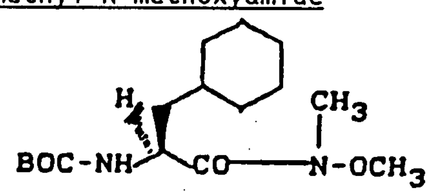


265 g (1.0 mole) of the compound from example I are dissolved in 2 l of methanol and hydrogenated over 20 g of 5% Rh/C for 5 h at 40 atm. The catalyst is pipetted off through celite, washed with methanol and the solution obtained concentrated. 271 g (100%) of example 6 are obtained.

NMR (DMSO, 300 MHz): δ = 0.8-1.8 (m, 22H, cyclohexylmethylene, $C(CH_3)_3$.

Example III

BOC cyclohexylalanine-N-methyl-N-methoxyamide

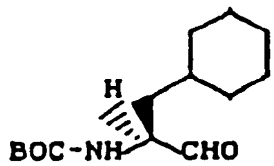


163.0 g (0.601 mole) of the compound of example II and 40.3 g (0.661 mole) of N,O-dimethylhydroxylamine are dissolved in 2 l of methylene chloride at room temperature. At 0°C, 303.5 g (3.005 mole) of triethylamine are added in drops (pH 8). At max. -10°C, 390.65 ml of 50% solution (0.601 mole) of n-propyl-phosphonic acid anhydride in methylene chloride are added in drops. Overnight it is warmed to 25°C and stirred for 16 h. Then the reaction solution is concentrated, the residue mixed with 500 ml of saturated bicarbonate solution and stirred 20 min. at 25°C. After extraction with acetic ester 3 times the organic phase is dried over Na_2SO_4 and concentrated. Crude yield: 178 g (94.6%). The crude substance is chromatographed on silica gel (eluent F). Yield: 136.69 (72.3%).

NMR (DMSO, 300 MHz): δ = 1.37 (s, 9H, $C(CH_3)_3$), 3.08 (s, 3H, N-CH_3); 3.71 (s, 3H, O-CH_3).

Example IV

BOC cyclohexylalaninal

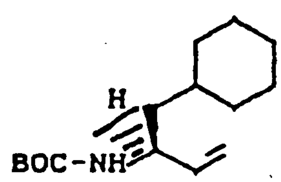


63.7 g (0.21 mole) of the compound of example III are dissolved in aloxated ether in a heated apparatus under nitrogen; at 0°C 10 g (0.263 mole) of $LiAlH_4$ are added to it in portions followed by stirring at 0°C for 20 min. Then a solution of 50 g (0.367 mole) of $KHSO_4$ in 1 l H_2O is added to it in drops at 0°C cautiously. The phases are separated, the aqueous phase extracted another 3 times with diethyl ether 300 ml, the combined organic phases washed 3 times with 3n HCl, 3 times with $NaHCO_3$ solution and 2 times with NaCl solution. The organic phase is dried over Na_2SO_4 and concentrated. Yield: 45 g (84.1%). The aldehyde is either further processed immediately or stored for 1 to 2 days at -24°C.

NMR (DMSO, 300 MHz): δ = 9.41 (s, 1H, -CHO).

Example V

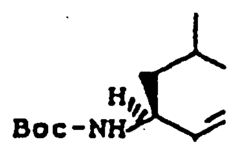
BOC allylamine



14.6 g (35 mmole) of "Instant Ylide" (Fluka 69500) are suspended in 90 ml of absolute tetrahydrofuran. With ice cooling at a reaction temperature between 20 and 25°C a solution of 9.0 g (35 mmole) of BOC cyclohexylalaninal in 45 ml of absolute tetrahydrofuran is added in drops. After 15 min. of stirring the reaction mixture is decanted onto 250 ml of ice and extracted twice with 150 ml of acetic ester/n-hexane 3:1 each time. After drying over Na_2SO_4 and concentrating the residue is chromato-graphed on silica gel (eluent D). Yield: 3.2 g (40.0%)
El-MS:m/z = 253 (0.1% M+H), 197 (9%).

Example VI

<u>BOC allylamine</u>

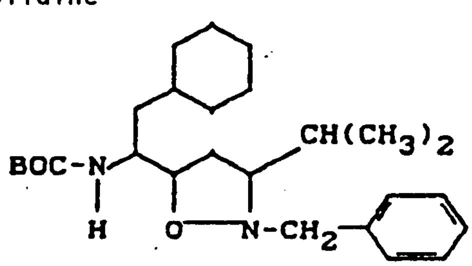


Synthesis according to the instructions of example V with a 0.24 mole batch.

Yield: 25.92 g (50.6%).

Example VII

2-benzyl-3(1-methylethyl)-5-[1-tert-butoxycarbonylamino-2-cyclohexylethyl]-isoxazolidine



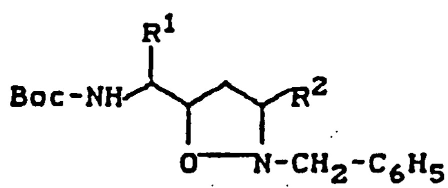
202.4 g (0.8 mole) of the compound of example V are dissolved in 100 ml of mesitylene and warmed to 140°C on the water separator. At this temperature of 197 g (1.6 mole) of N-benzylhydroxylamine and 137.68 g (1.6 mole) of isobutyraldehyde in 800 ml of mesitylene are added in drops over 2 h. After 4 h and 8 h of reaction time the same quantity of N-benzylhydroxyl-amine, isobutyraldehyde in mesitylene are added in drops. After a total of 16 h reaction time the batch is concentrated, the residue mixed with diethyl ether and then washed with 1 m $KHSO_4$ solution. After drying over Na_2SO_4 and concentrating it was chromatographed on silica gel (eluent B).
Yield: 168 (52.2% of the theory)

4 diastereomers were obtained:

Diastereomer	Yield	DC, R_f (B)	^{1}H-NMR C-4-NH
a) 1S 2S 4S	11 g	0.42	6.37
b) 1R 3R 4S	10 g	0.29	6.57
c) 1R 3S 4S	69 g	0.25	6.41
d) 1S 3R 4S	34 g	0.18	6.63

The examples listed in Table I were synthesized according to the instructions of example VII

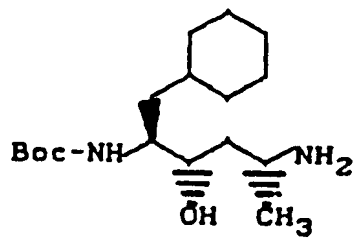
Table I



Example No.	R^1	R^2	FAB-MS M+H[%]
VIII	$-CH_2-CH(CH_3)_2$	$-CH(CH_3)_2$	391 (55 Isomer B
IX	$-CH_2-C_6H_{11}$	$-CH_3$	403 (51)

Example X

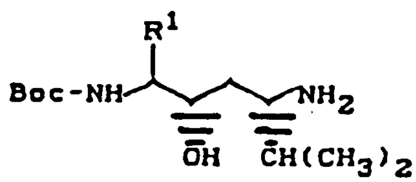
(2R, 4S, 5S)-2-amino-5-(tert-butoxycarbonylamino)-6-cyclohexyl-4-hydroxyhexane



18.1 g (45 mmole) of the compound of example IX (diastereomer C) are dissolved in 300 ml of methanol. After addition of 14.2 g (225 mmole) of ammonium formate, it is flushed intensively with N_2 and 3.6 g of palladium/carbon (10%) added. It is stirred for 3 hours on reflux. After cooling the catalyst is filtered off, the solution concentrated, dissolved in acetic acid ethyl ester and washed twice with saturated bicarbonate solution. The organic phase is dried over sodium sulfate, filtered, concentrated and dried in the high vacuum. Yield: 11.36 g (80.3% of the theory) R_f = 0.27 (I).

The compounds listed in Table II were synthesized according to the instructions of example X.

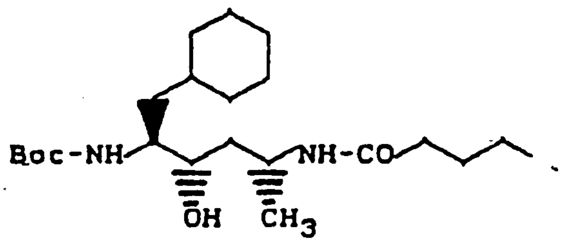
Table II



Example No.	R^1	FAB-MS M+H (%)
XI	$-CH_2-CH(CH_3)_2$	303 (95)
XII	$-CH_2-C_6H_{11}$	343 (100)

Example XIII

(2R, 4S, 5S)-2-(valerylamino)-5-(tert-butoxycarbonylamino)-6-cyclohexyl-4-hydroxyhexane



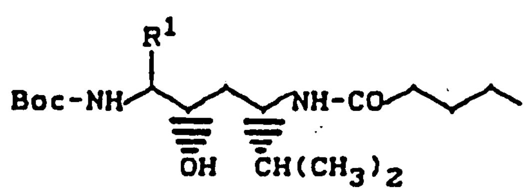
6.6 g (21 mmole) of the compound of example X are dissolved in 500 ml of methylene chloride. With exclusion of moisture ($CaCl_2$ tube) a solution of pentanic acid anhydride [prepared from 2.16 g (21 mmole) of pentanic acid and 2.16 g (10.5 mmole) of dicyclohexylcarbodiimide in 50 ml of methylene chloride, filtration] in methylene chloride are added at room temperature. After 3 h it is concentrated, absorbed in acetic acid ethyl ester, washed with saturated bicarbonate solution and dried over sodium sulfate. After filtration and concentration it is dried in a high vacuum.

Yield: 8.0 g (95.2% of the theory). R_f = 0.74 (G).

FAB-MS:m/z = 421 (12%, M+Na).

The compounds listed in Table III were synthesized according to the instructions of example XIII.

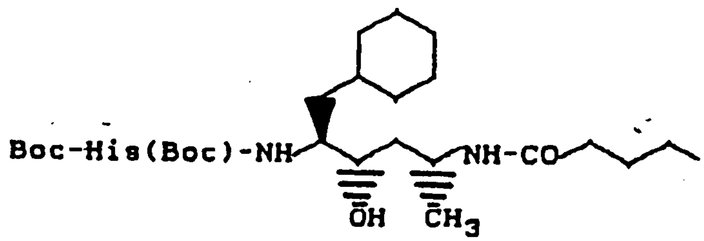
Table III



Example No.	R^1	FAB-MS M+H [%]
XIV	$-CH_2-CH(CH_3)_2$	387 (100)
XV	$-CH_2-C_6H_{11}$	327 (3, M+H-Boc)

Example XVI

(2R, 4S, 5S)-2-(valerylamino)-5-[Nα-(tert-butoxycarbonyl)-Nπ-(tert.butoxycarbonyl)-L-histidylamino]-6-cyclohexyl-4-hydroxyhexane



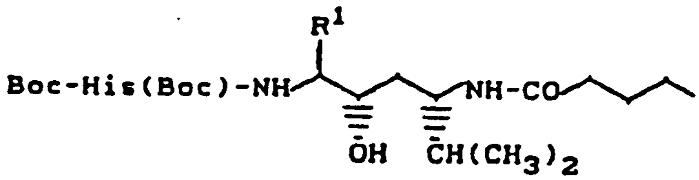
7.57 g (19 mmole) of the compound of example XIII are stirred in 70 ml of 4 n hydrochloric acid/dioxane for 30 min. with exclusion of moisture. The solution is concentrated, mixed with diethyl ether and concentrated until dry. After drying in the high vacuum, 5.54 g (16.5 mmole) of the corresponding hydrochloride, 4.46 g (33 mmole) of HOBT and 5.86 g (16.5 mmole) of Boc-His(Boc)OH dissolved in 500 ml of methylene chloride are dissolved. After cooling to 0°C it is adjusted with N-methylmorpholine to pH 8.5, and 3.57 g (17.3 mmole) of dicyclohexylcarbodiimide are added. After 16 h at 20°C the urea is filtered off, the solution concentrated, absorbed in acetic acid ethyl ester and washed with saturated bicarbonate solution. After drying over sodium sulfate it is concentrated and dried in the high vacuum.

Yield: 8.33 g (79.5% of the theory). R_f = 0.61 (G).

FAB-MS:m/z = 636 (79%, M+H).

The examples listed in Table IV were synthesized by analogy with the instructions of example XVI.

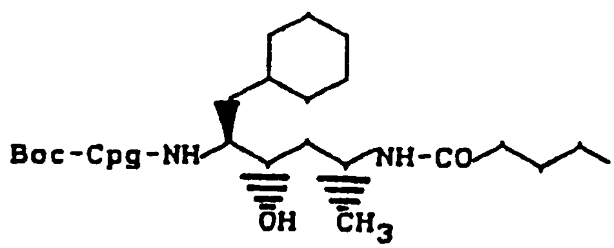
Table IV



Example No.	R^1	FAB-MS M+H [%]
XVII	$-CH_2-CH(CH_3)_2$	624 (16)
XVIII	$-CH_2-C_6H_{11}$	670 (44, M+Li)

Example XIX

(2R, 4S, 5S)-2-(valerylamino)-5-[Nα-(tert-butoxycarbonyl)-L-cyclopentylglycylamino]-6-cyclohexyl-4-hydroxyhexane



5.6 g (24.4 mmole) of BocCpgOH are dissolved in 50 ml of absolute tetrahydrofuran. After addition of 2.7 ml (24.4 mmole) of N-methylmorpholine at -20°C, 3.2 ml (24.4 mmole) of chloroformic acid isobutyl ester are added in drops and stirred for 15 min. at -20°C. To this solution, 5.45 g (16.3 mmole) of the deblocked compound of example XIII and 1.8 ml (16.3 mmole) of N-methylmorpholine in 50 ml of tetrahydrofuran/water 1:1 are added in drops and within 30 min. warmed to 20°C. After another 30 min. the reaction solution is concentrated, added to 1 l of diethyl ether and cooled to 0°C. After 16 h, 4.6 g (54.0%) of crystals are pipetted off. The mother liquor is washed with saturated bicarbonate solution, the ether phase dried over sodium

sulfate, concentrated and dried in the high vacuum. 6 g of a yellow oil are obtained which is chromatographed on silica gel (E).

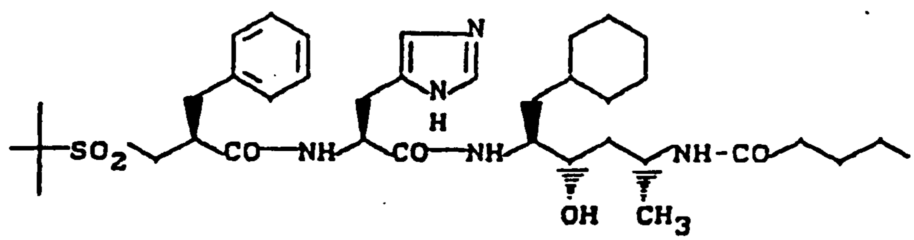
Yield: 3.31 g (38.8% of the theory) R_f = 0.79 (G).

FAB-MS:m/z = 524 (38%, M+H).

Production examples

Example 1

(2R, 4S, 5S)-2-(valerylamino)-5-[Nα-(2-S-benzyl-3-tert-butylsulfonylpropionyl)-L-histidylamino]--6-cyclohexyl-4-hydroxyhexane

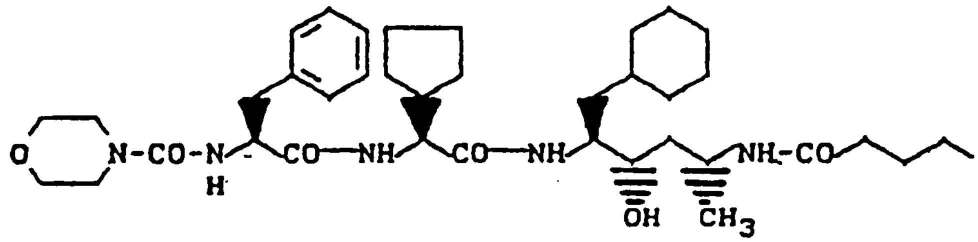


1.145 g (1.8 mmole) of the compound of example XVI are stirred in 1 ml of 4 n hydrochloric acid/dioxane for 30 min. The solution is concentrated, mixed with diethyl ether and concentrated until dry. After drying in the high vacuum, 875.5 mg (1.8 mmole) of the dihydrochloride formed are dissolved in 50 ml of methylene chloride and cooled to 0°C. After addition of 509.4 mg (1.8 mmole) of β-tert-butylsulfonyl-α-benzylpropionic acid it is adjusted to pH 8 with triethylamine and mixed with 875.2 mg (1.98 mmole) of BOP. After 16 h of reaction at room temperature it is concentrated, absorbed in acetic acid ethyl ester and washed 3 times with saturated bicarbonate solution. 494.8 mg (39.2% of the theory) are obtained, which are chromatographed on silica gel (G).

R_f = 0.24 (G). FAB-MS:m/z = 702 (100%, M+H).

Example 2

(2R, 4S, 5S)-2-(valerylamino)-5-{Nα-[4-(morpholinocarbonyl)-L-phenylalanyl]-L-cyclopentylglycylamino}-6-cyclohexyl-4-hydroxyhexane



1.044 g (3.75 mmole) of morpholinocarbonyl-phenylalanine are dissolved in 50 ml of absolute tetrahydrofuran. After addition of 0.4 ml (3.75 mmole) of N-methylmorpholine, at -20°C, 0.48 ml (3.75 mmole) of chloroformic acid isobutyl ester are added in drops and stirred for 15 min. at -20°C. In this solution, 1.17 g (2.5 mmole) of the deblocked compound from example XIX in 50 ml of tetrahydrofuran/water 1:1 [adjusted to pH 8 with N-methylmorpholine] are added in drops and warmed for 16 h at 20°C. The refining is performed as described in example XIX.

Crystals: 944.5 mg (55.5% of the theory)

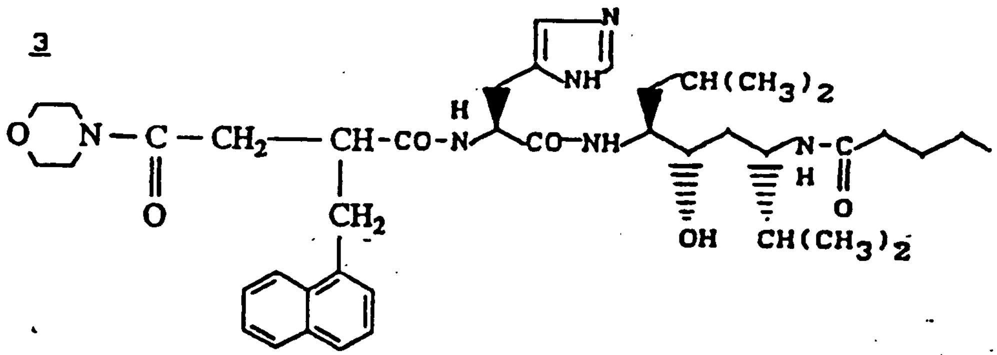
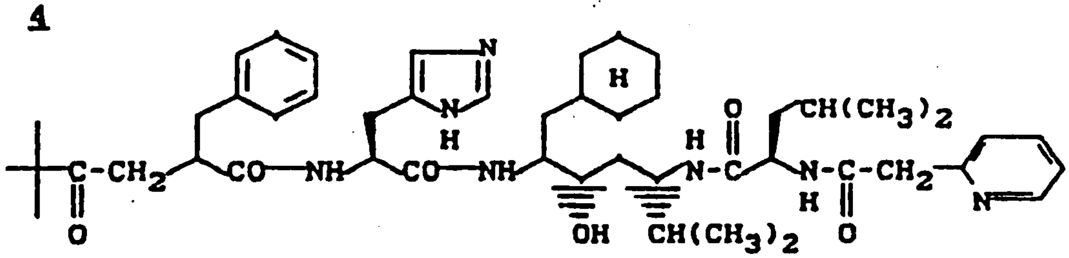
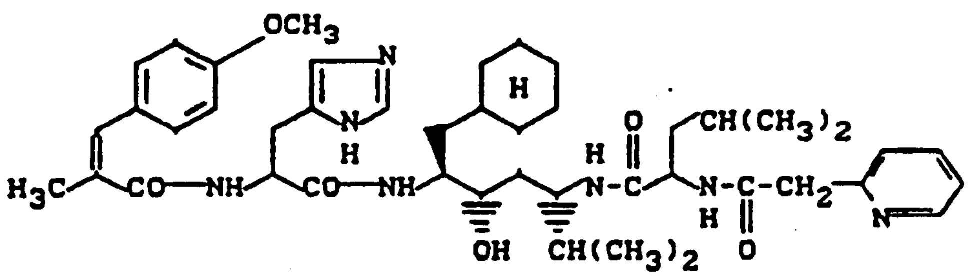
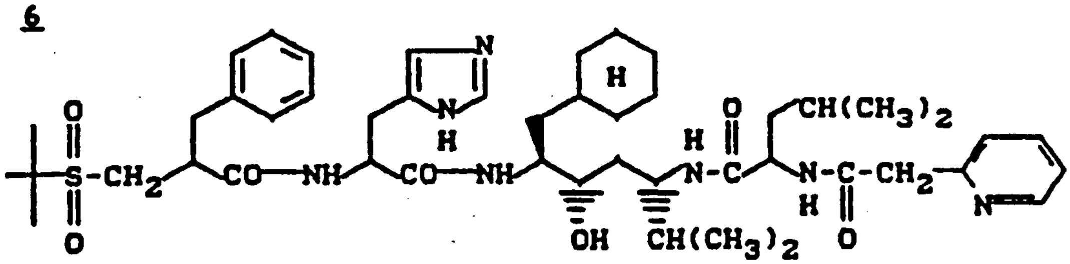
Oil 800 mg: after column chromatography 108.2 mg (6.4% of the theory)

Total yield: 1.053 g (64.9% of the theory). R_f = 0.62 (G).

FAB-MS:m/z = 624 (100% M+H).

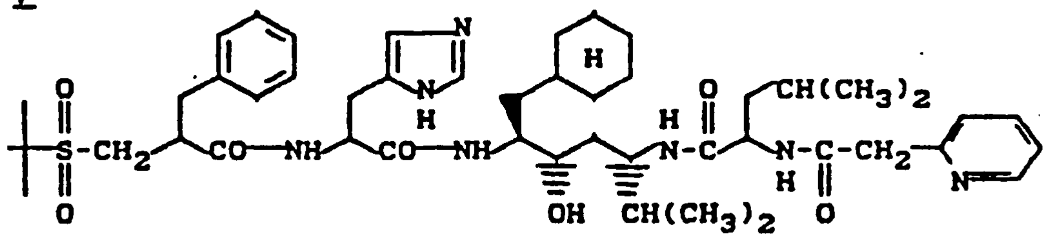
The examples listed in Table I were synthesized by analogy with the instructions of example 1.

Table 1

Example No.	Formula
3	
NMR: X FAB-MS: 723 (100%, M+J)	Empirical formula: $C_{41}H_{60}O_6$ R_f = 0.41 (I)
4	
NMR: X FAB-MS: 842 (61%, M+H)	Empirical formula: $C_{48}H_{71}N_7O_6$ R_f: 0.22 (G)
5	
NMR: X FAB-MS: 786 (53%, M+H)	Empirical formula $C_{44}H_{63}N_7O_6$ R_f: 0.38 (G)
6	
NMR: X FAB-MS: 878 (100%, M+H)	Empirical formula: $C_{47}H_{71}N_7O_7S$ R_f: 0.37 (I) Isomer (a)

Example No.	Formula

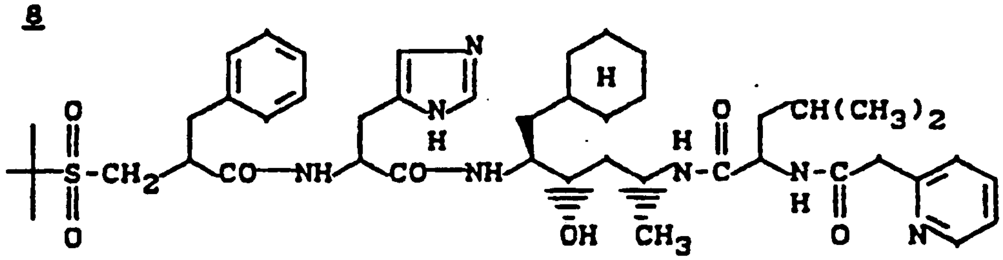
7



NMR: X
FAB-MS: 878 (50%, M+H)

Empirical formula: $C_{47}H_{71}N_7O_7S$
R_f: 0.37 (I) Isomer (b)

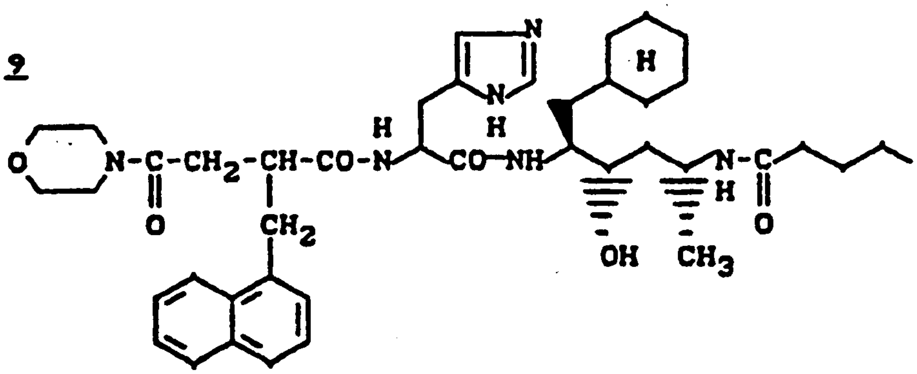
8



NMR: X
FAB-MS: 850 (100% M+H)

Empirical Formula: $C_{45}H_{67}N_7O_7S$
R_f: 0.42 (I)

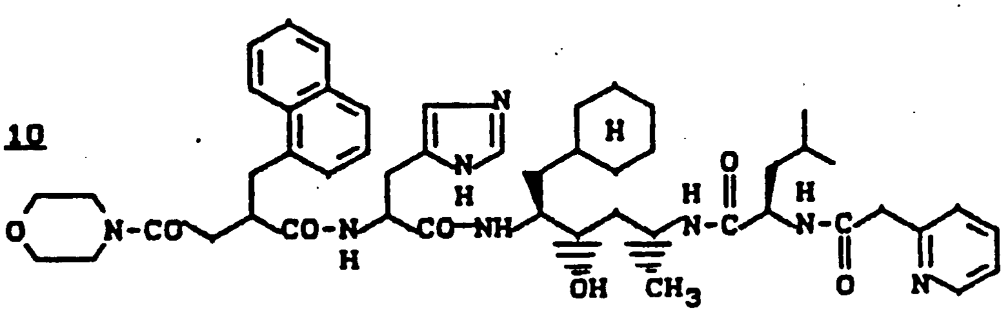
9



NMR: X
FAB-MS: 745 (61%, M+H)

Empirical formula: $C_{42}H_{60}N_6O_6$
R_f = 0.32 (I)

10

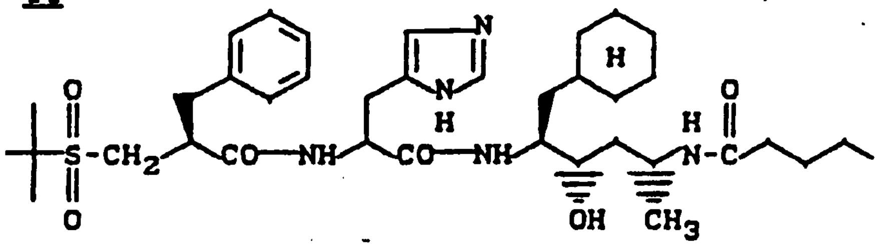


NMR: X
FAB-MS: 893 (30%, M+H)

Empirical formula: $C_{50}H_{86}N_8O_7$
R_f = 0.48 (I)

Example No.	Formula

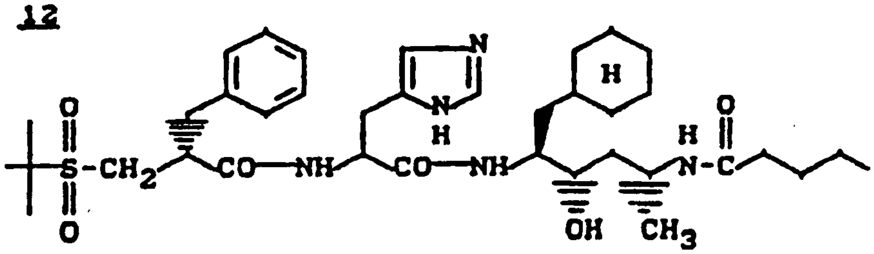
11



NMR: X
FAB-MS: 702 (100% M+H)

Empirical formula: $C_{37}H_{59}N_5O_6S$
R_f: 0.24 (G)

12



NMR: X
FAB-MS: 702 (31%, M+H)

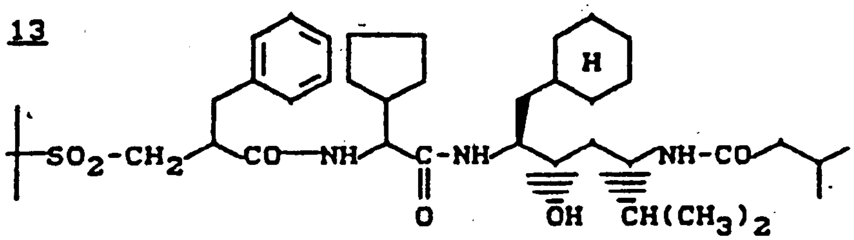
Empirical formula: $C_{37}H_{59}N_5O_6S$
R_f: 0.38 (G)

The compounds listed in Table 2 were synthesized by analogy with the instructions of example 2.

Table 2

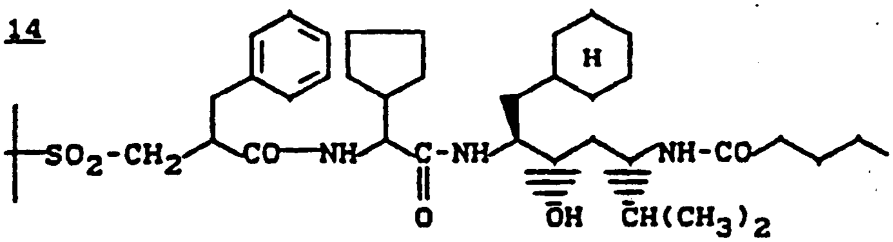
Example No.	Formula

13



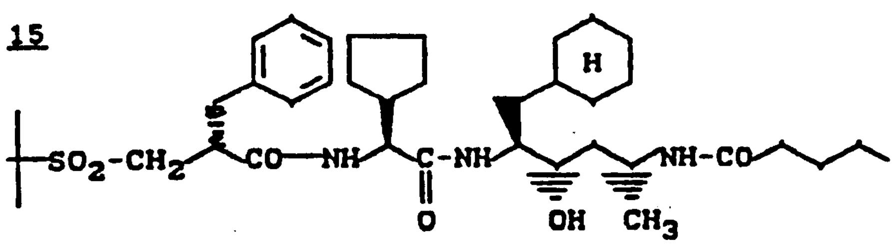
NMR: X	Empirical formula: $C_{40}H_{67}N_3O_6S$
FAB-MS: 718 (90%, M+H)	

14



NMR: X	Empirical formula: $C_{40}H_{67}N_3O_6S$
FAB-MS: 718 (100% M+H)	

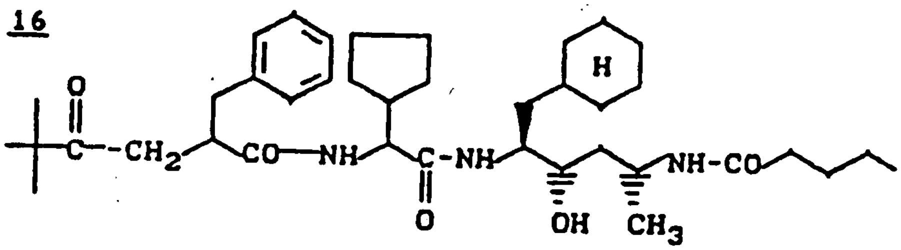
15



NMR: X	Empirical formula: $C_{38}H_{63}N_3O_6S$
FAB-MS: 690 (75%, M+H)	R_f = 0.33 (M)

Example No.	Formula

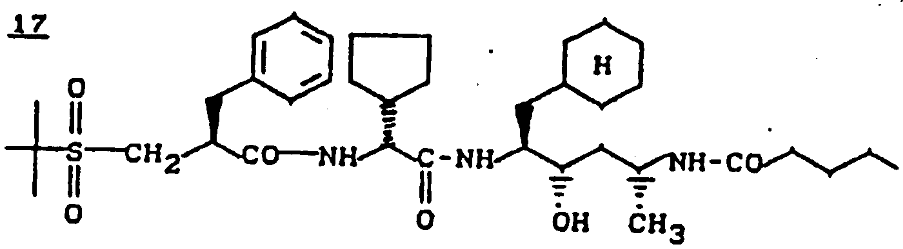
16



NMR: X
FAB-MS: 654 (100% M+H)

Empirical formula: $C_{39}H_{63}N_3O_5$
R_f = 0.60 (G)

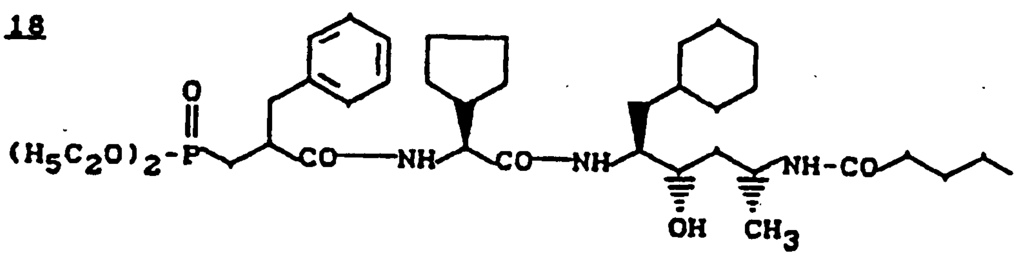
17



NMR: X
FAB-MS: 690 (100% M+H)

Empirical formula: $C_{38}H_{63}N_3O_6S$
R_f = 0.42 (M)

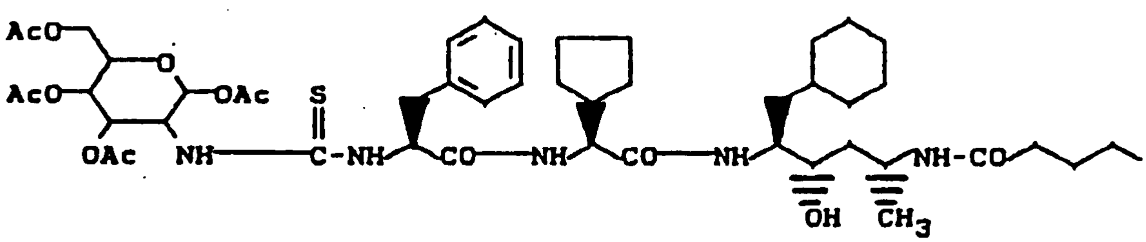
18



NMR: X
FAB-MS: 705 (100%)

Empirical formula: $C_{38}H_{64}N_3O_6P$
R_f = 0.58 (G)

19

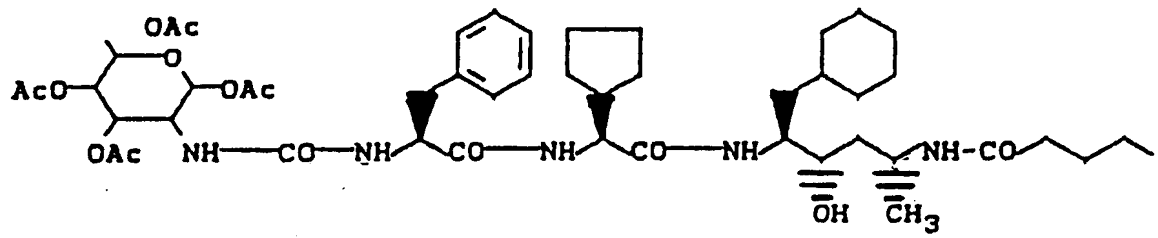


NMR: X
FAB-MS: 966 (10%, M+Li)

Empirical formula: $C_{48}H_{73}N_5O_{13}S$
R_f = 0.69 (G)

Example No.	Formula

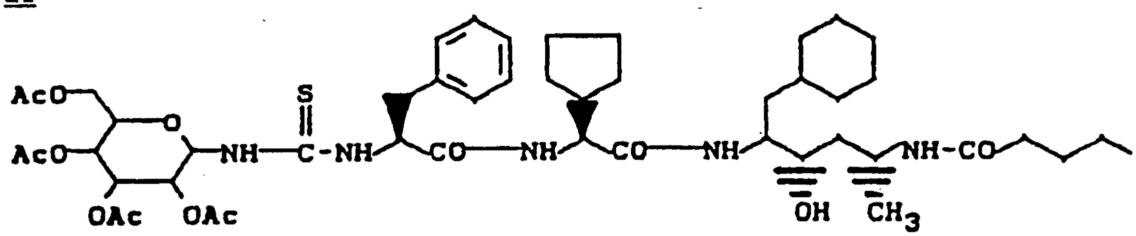
20



NMR: X
FAB-MS: 950 (40)%, M+Li)

Empirical formula: $C_{48}H_{73}N_5O_{14}$
R_f = 0.64 (G)

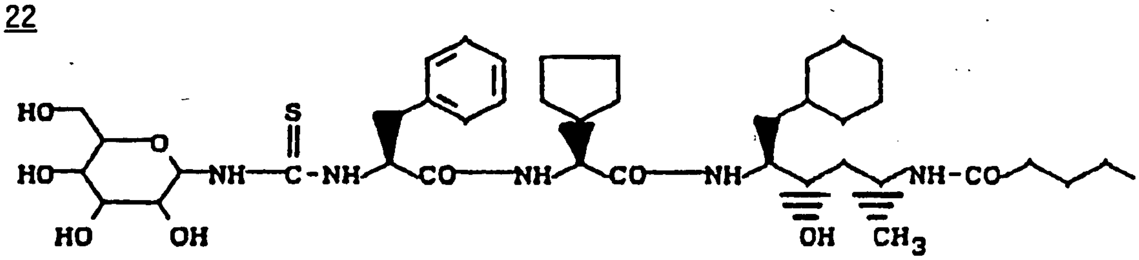
21



NMR: X
FAB-MS: 966 (100%, M+Li)

Empirical formula: $C_{48}H_{73}N_5O_{13}S$
R_f = 0.44 (G)

22

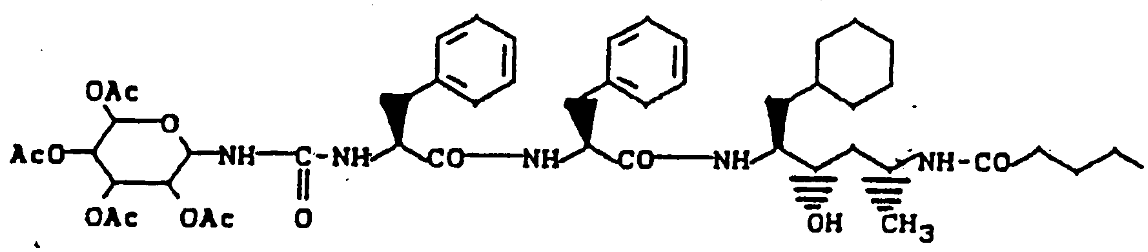


NMR: X
FAB-MS: 798 (M+Li)

Empirical formula: $C_{40}H_{65}N_5O_9S$
R_f = 0.53 (G)

Example No.	Formula

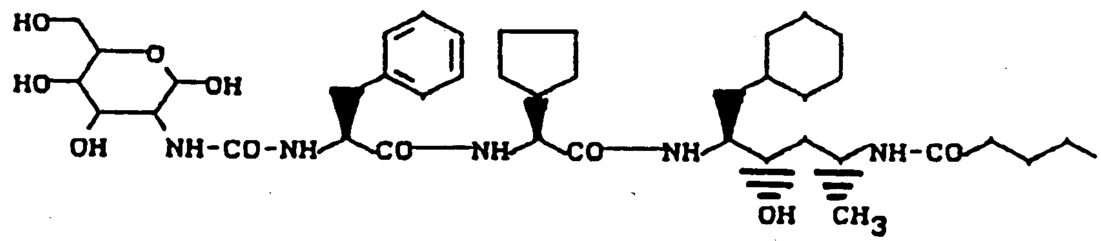
23



NMR: X
FAB-MS: 746 (100%, M+Li)

Empirical formula: $C_{40}H_{65}N_5O_9S$
R_f = 0.53 (G)

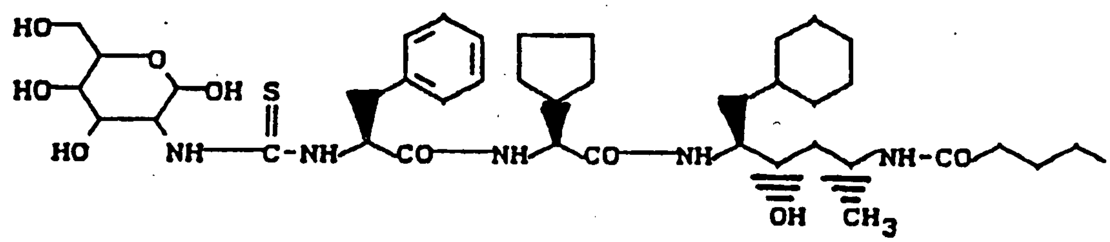
24



NMR: X
FAB-MS: 746 (100%, M+Li)

Empirical formula: $C_{40}H_{61}N_5O_8$
R_f = 0.40 (G)

25

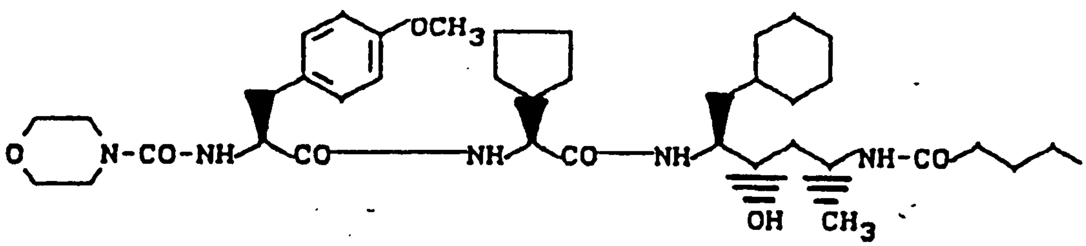


NMR: X
FAB-MS: 780 (100%, M+Li)

Empirical formula: $C_{40}H_{63}N_5O_8S$
HPLC

Example No.	Formula

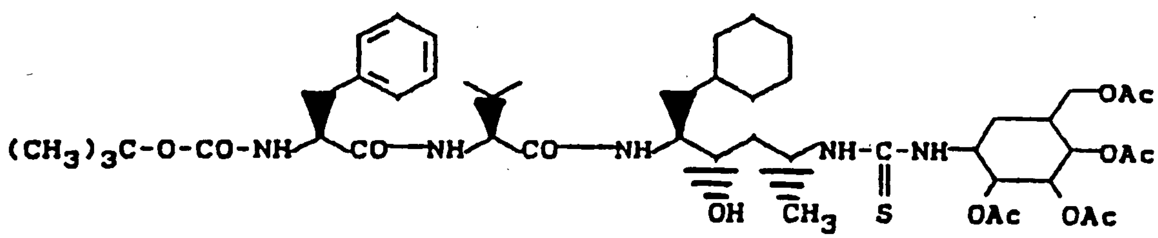
26



NMR: X
FAB-MS: 714 (75% M+H)

Empirical formula: $C_{39}H_{63}N_5O_7$
R_f = 0.39 (G)

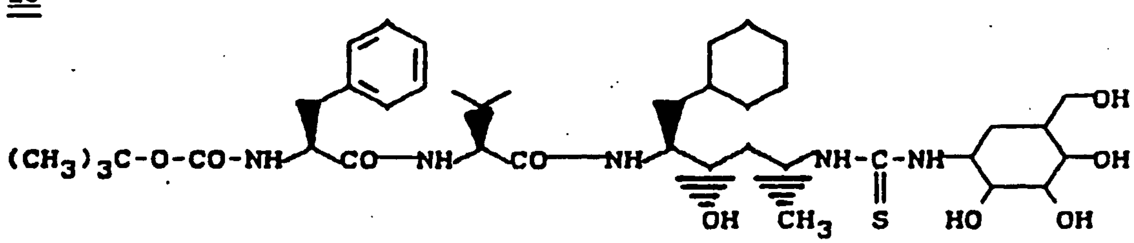
27



NMR: X
FAB-MS: 950 (10% M+H)

Empirical formula: $C_{46}H_{71}N_5O_{24}S$
R_f = 0.43 (G)

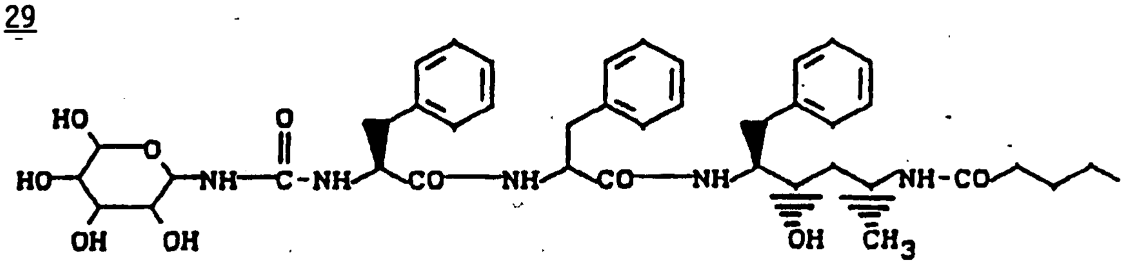
28



NMR: X
FAB-MS: 782 (87% M+H)

Empirical formula: $C_{38}H_{63}N_5O_{10}S$
R_f = 0.19 (G)

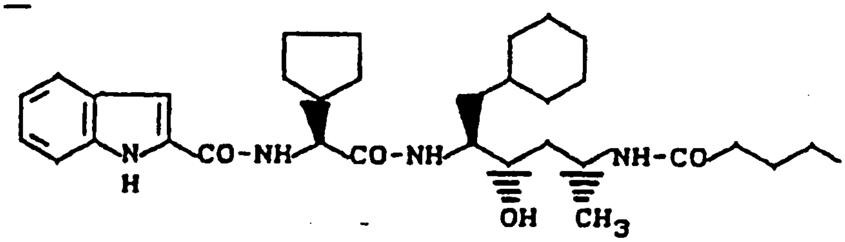
29



NMR: X
FAB-MS: 784 (95% M+H)

Empirical formula: $C_{41}H_{61}N_5O_{10}$
R_f = 0.12 (G)

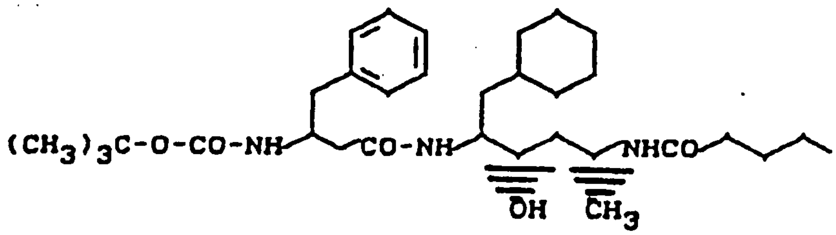
Example No.	Formula
30	



NMR: X
FAB-MS: 573 (23% M+Li)

Empirical formula: $C_{23}H_{50}N_4O_4$
R_f = 0.35 (I)

31

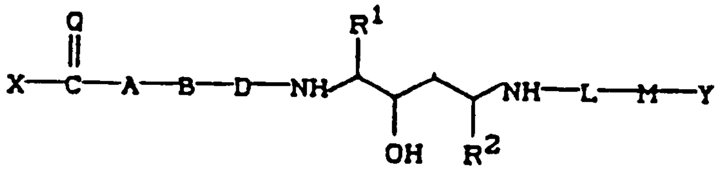


NMR: X
FAB-MS: 566 (100% M+Li)

Empirical formula: $C_{32}H_{53}N_3O_5$
R_f = 0.51 (G)

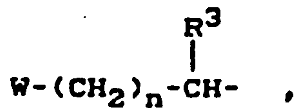
Claims

1. Retroisosteric acylated dipeptides of general formula (I)

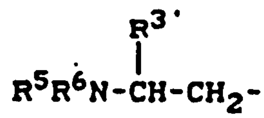


(I)

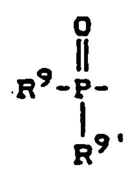
in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula



R^4-NH-,

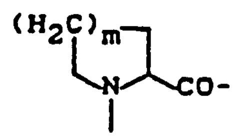


or for T, where R^3 and $R^{3'}$ are the same or different and signify straight chained or branched alkyl with up to 8 carbons atoms which is possibly substituted by aryl with 6 to 10 carbons atoms, n signifies the number 1, 2, 3 or 4, W is a group of the formula R^7-CO-, R^8-SO_2- or

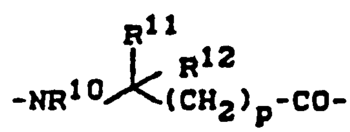


where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 8 carbons atoms or a 6-membered heterocycle with up to 3 heteroatoms from the series nitrogen, oxygen or sulfur,
R^9 and $R^{9'}$ are the same or different and denote hydroxy or alkoxy with up to 8 carbons atoms,

R^4 is a carbohydrate radical with 4 to 8 carbons atoms, the OH functions of the sugar possibly being shielded, Q signifies oxygen or sulfur, R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 8 carbons atoms, phenyl or an amino protective group, T is a straight chained or branched alkenyl with up to 8 carbon atoms which is possibly substituted by aryl with 6 to 10 carbon-atoms which in turn may be substituted by halogen, hydroxy or alkoxy with up to 6 carbon atoms, A, B, and D are the same or different and stand for a direct bond or for a radical of the formula:

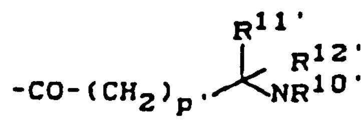


where m signifies the number 1 or 2 or stands for a group of the formula



where p signifies the number 0 or 1, R^{10} denotes hydrogen, straight chained or branched alkyl with up to 6 carbon atoms or an amino protective group, R^{11} and R^{12} are the same or different and denote: hydrogen or cycloalkyl with 3 to 8 carbon atoms, or a 3 to 8 membered heterocycle with up to 4 heteroatoms from the series of nitrogen, oxygen or sulfur, a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by alkylthio with up to 6 carbon atoms, hydroxy, mercapto, guanidyl or by a group of the formula $-NR^5R^6$ or $R^{13}-OC$,
where R^5 and R^6 have the above-reported meaning, and

R^{13} denotes a hydroxy, benzyloxy, alkoxy with up 6 carbon atoms or the above-listed group $-NR^5R^6$ or which is possibly substituted by aryl with 6 to 10 carbon atoms which in turn may be substituted by hydroxy, halogen, nitro, alkoxy with up to 8 carbon atoms or by the group $-NR^5R^6$,
where R^5 and R^6 have the above-given meaning or which may possibly be substituted by a 5 or 6-membered nitrogen-containing heterocycle or indolyl, where the corresponding -NH- functions may possibly be shielded by alkyl with up to 6 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula



where p', $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the above-reported meaning for p, R^{10}, R^{11} and R^{12}, in their D or L form or as a D,L isomer mixture,
R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms, Y stands for a group of the formula

$$-\overset{\displaystyle Q}{\overset{\|}{C}}-NH-R^4$$

or for $-CO-R^{14}$, where Q and R^4 have the above-reported meaning,
R^{14} is a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by pyridyl, phenyl or the group $-NR^{15}R^{16}$
where R^{15} and R^{16} either have the above-reported meaning of R^5 and R^6 and are the same as or different from these, or R^{15} denotes hydrogen and
R^{16} the group of the formula

$$\begin{array}{c} R^3 \\ | \\ -CO-CH-(CH_2)_n-W \end{array} \quad \text{or} \quad \begin{array}{c} Q \\ \| \\ -C-N-R^4 \\ H \end{array}$$

where W, Q, n, R^3 and R^4 have the above reported meaning, and their physiologically unobjectionable salts, with the qualification that X may signify tert-butoxy only when Y stands for the group Q

$$\begin{array}{c} Q \\ \| \\ -C-NH-R^4 \end{array} \quad \text{or}$$

2. Compounds of the general formula (I) as in claim 1 in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula:

$$W-(CH_2)_n-\overset{\displaystyle R^3}{\overset{|}{C}}H- \;, \quad R^4-\underset{H}{N}- \;, \quad R^5R^6N-\overset{\displaystyle R^{3'}}{\overset{|}{C}}H-CH_2-$$

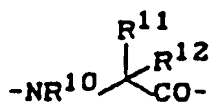
or for T, where R^3 and $R^{3'}$ are the same or different and signify a straight chained or branched alkyl with up to 6 carbon atoms which may possibly be substituted by phenyl or naphthyl, n is a number 1, 2, or 3, W is a group of the formula R^7-CO-, R^8-SO_2- or

$$\begin{array}{c} O \\ \| \\ R^9-P- \\ | \\ R^{9'} \end{array}$$

where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 6 carbon atoms or morpholino,
R^9 and $R^{9'}$ are the same or different and signify hydroxy or alkoxy with up to 6 carbon atoms,

R^4 signifies a pyranosyl radical, where the OH function of the sugar may possibly be protected, Q denotes oxygen or sulfur,
R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 6 carbon atoms or an amino protective group, T is a straight chained or branched alkenyl with up to 6 carbon atoms which is possibly substituted by phenyl which in turn may be substituted by fluorine, chlorine, hydroxy or alkoxy with up to 4 carbon atoms, A, B and D are the same or different and stand for:

- a direct bond, or
- for proline, or
- for a group of the formula



where R^{10} denotes hydrogen or a straight chained or branched alkyl with up to 4 carbon atoms,
R^{11} and R^{12} are the same or different and denote cyclopentyl, cyclohexyl, hydrogen or straight chained or branched alkyl with up to 6 carbon atoms which may possibly be substituted by naphthyl or phenyl, which in turn may be substituted by fluorine, chlorine, nitro or alkoxy with up to 6 carbon atoms, or is substituted by indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, where the corresponding -NH functions may possibly be substituted by alkyl with up to 4 carbon atoms or by an amino protective group,
L and M are the same or different and stand for a direct bond or for a group of the formula

where $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the above-reported meaning for R^{10}, R^{11} and R^{12} and are the same as or different from these, in their D or L form or as a D,L isomer mixture, R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl, Y for a group of the formula

$$-\overset{\overset{\large Q}{\|}}{C}-NH-R^4$$

or stands for $-CO-R^{14}$, where Q and R^4 have the above-reported meaning, R^{14} is a straight chained or branched alkyl with up to 6 carbon atoms which is possibly substituted by pyridyl, phenyl or by the group $-NR^{15}R^{16}$, where R^{15} and R^{16} are either the same or different and which have the above-given meaning of R^5 and R^6 and are the same as or different from these or R^{15} signifies hydrogen and R^{16} a group of the formula

$$-CO-\overset{\overset{\large R^3}{|}}{CH}-(CH_2)_n-W$$

or

$$-\overset{\overset{\large Q}{\|}}{C}-NH-R^4$$

where W, Q, n, R^3 and R^4 have the above-given meaning, and their physiologically unobjectionable salts with the qualification that X may signify tert-butoxy only if Y stands for the group Q

$$-\overset{\displaystyle O}{\overset{\|}{C}}-NH-R^4 \quad \text{or} \quad -CO$$ 

3. Compounds of general formula (I) as in claim 1 in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula

$$W-(CH_2)_n-\overset{\displaystyle R^3}{\overset{|}{CH}}- \ ,$$

R^4-NH-,

$$R^5R^6-N-\overset{\displaystyle R^{3'}}{\overset{|}{CH}}-CH_2-$$

or for T, where R^3 and $R^{3'}$ are the same or different and denote straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by phenyl or naphthyl,

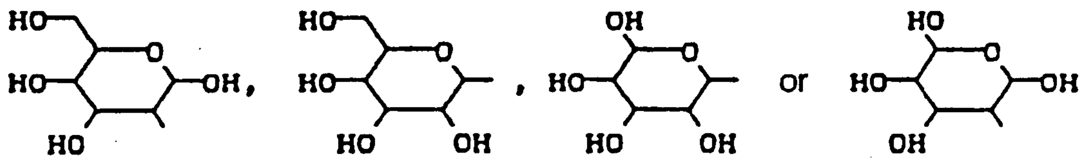
n is a number 1 or 2, W is a group of the formula R^7-CO- R^8-SO_2- or

$$R^9-\underset{\underset{\displaystyle R^{9'}}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}}-$$

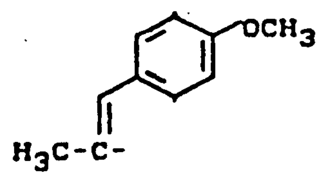
where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 4 carbon atoms or morpholino,

R^9 and $R^{9'}$ are the same or different and denote hydroxy or alkoxy with up to 4 carbon atoms,

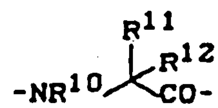
R^4 is a radical of the formula



where the OH functions are possibly protected by acetyl, Q signifies oxygen or sulfur, R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 4 carbon atoms or an amino protective group, T denotes the radical of the formula



A, B and D are the same or different and stand for: a direct bond, or for proline, or for a group of the formula



where R^{10} denotes hydrogen or methyl,

R^{11} and R^{12} are the same or different and signify cyclopentyl or straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by naphthyl or phenyl which in turn may be substituted by fluorine, chlorine, or alkoxy with up to 4 carbon atoms, or alkyl is substituted by imidazolyl, triazolyl, pyridyl or pyrazolyl, where the -NH functions are possibly protected by methyl, Boc or BOM, L and M are the same or different and stand for a direct bond or for a group of the formula

where $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the meaning reported above for R^{10}, R^{11} and R^{12} and are the same as or different from these, in their D or L form or as a D,L isomer mixture,

R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 4 carbon atoms possibly substituted by cyclohexyl or phenyl,

Y stands for a group of the formula

$$-\overset{\overset{\displaystyle Q}{\|}}{C}-NH-R^4$$

or for $-CO-R^{14}$, where Q and R^4 have the above-given meaning,

R^{14} is a straight chained or branched alkyl with up to 4 carbon atoms which is possibly substituted by pyridyl, phenyl or by the group $-NR^{15}R^{16}$ in which

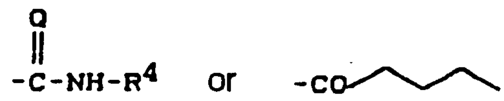
R^{15} signifies hydrogen and R^{16} a group of the formula

$$-CO-\overset{\overset{\displaystyle R^3}{|}}{CH}-(CH_2)_n-W$$

or

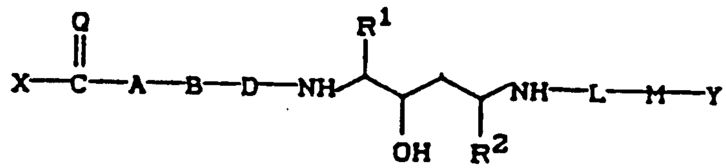
$$-\overset{\overset{\displaystyle Q}{\|}}{C}-NH-R^4$$

where W, Q, n, R^3 and R^4 have the above-reported meaning, and their physiologically unobjectionable salts with the qualification that X may signify tert-butoxy only when Y stands for the group Q



4. Compounds of general formula (I) as in claim 1 for use in control of diseases.

5. Process for synthesis of retroisosteric dipeptides of general formula (I)



(I)

in which X stands for indolyl, tert-butoxy, morpholino or for a group of the formula

$$W\text{-}(CH_2)_n\text{-}\underset{}{CH}(R^3)\text{-}\ ,$$

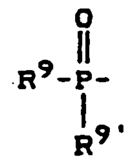
R^4-NH-,

$$R^5R^6\text{-}N\text{-}CH(R^{3'})\text{-}CH_2\text{-}$$

or for T, where R^3 and $R^{3'}$ are the same or different and signify straight chained or branched alkyl with up to 8 carbons atoms which is possibly substituted by aryl with 6 to 10 carbons atoms,

n signifies the number 1, 2, 3 or 4,

W is a group of the formula R^7-CO-, R^8-SO_2- or

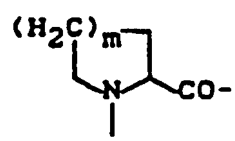


where R^7 and R^8 are the same or different and signify straight chained or branched alkyl with up to 8 carbons atoms or a 6-membered heterocycle with up to 3 heteroatoms from the series nitrogen, oxygen or sulfur,

R^9 and $R^{9'}$ are the same or different and denote hydroxy or alkoxy with up to 8 carbons atoms,

R^4 is a carbohydrate radical with 4 to 8 carbons atoms, the OH functions of the sugar possibly being shielded, Q signifies oxygen or sulfur,

R^5 and R^6 are the same or different and signify hydrogen, straight chained or branched alkyl with up to 8 carbons atoms, phenyl or an amino protective group, T is a straight chained or branched alkenyl with up to 8 carbon atoms which is possibly substituted by aryl with 6 to 10 carbon atoms which in turn may be substituted by halogen, hydroxy or alkoxy with up to 6 carbon atoms, A, B, and D are the same or different and stand for a direct bond or for a radical of the formula:



where m signifies the number 1 or 2 or stands for a group of the formula

where p signifies the number 0 or 1,

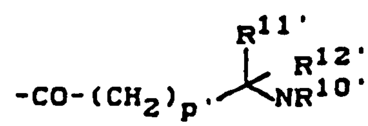
R^{10} denotes hydrogen, straight chained or branched alkyl with up to 6 carbon atoms or an amino protective group,

R^{11} and R^{12} are the same or different and denote: hydrogen or cycloalkyl with 3 to 8 carbon atoms, or a 3 to 8 membered heterocycle with up to 4 heteroatoms from the series of nitrogen, oxygen or sulfur, a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by alkylthio with up to 6 carbon atoms, hydroxy, mercapto, guanidyl or by a group of the formula $-NR^5R^6$ or R^{13}-OC,

where R^5 and R^6 have the above-reported meaning, and

R^{13} denotes a hydroxy, benzyloxy, alkoxy with up 6 carbon atoms or the above-listed group $-NR^5R^6$, or which is possibly substituted by aryl with 6 to 10 carbon atoms which in turn may be substituted by hydroxy, halogen, nitro, alkoxy with up to 8 carbon atoms or by the group $-NR^5R^6$,

where R^5 and R^6 have the above-given meaning or which may possibly be substituted by a 5 or 6 membered nitrogen-containing heterocycle or indolyl, where the corresponding -NH- functions may possibly be shielded by alkyl with up to 6 carbon atoms or by an amino protective group, L and M are the same or different and stand for a direct bond or for a group of the formula



where p', $R^{10'}$, $R^{11'}$ and $R^{12'}$ have the above-reported meaning for p, R^{10}, R^{11} and R^{12}, in their D or L form or as a D,L isomer mixture,

R^1 and R^2 are the same or different and stand for a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by cycloalkyl with 3 to 8 carbon atoms or aryl with 6 to 10 carbon atoms,
Y stands for a group of the formula

$$-\overset{\overset{\large Q}{\|}}{C}-NH-R^4$$

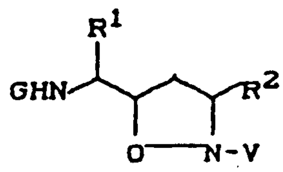
or for $-CO-R^{14}$, where Q and R^4 have the above-reported meaning,
R^{14} is a straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by pyridyl, phenyl or the group $-NR^{15}R^{16}$
where R^{15} and R^{16} either have the above-reported meaning of R^5 and R^6 and are the same as or different from these, or
R^{15} denotes hydrogen and R^{16} the group of the formula

$$-CO-\overset{\overset{\large R^3}{|}}{C}H-(CH_2)_n-W \quad \text{or} \quad -\overset{\overset{\large Q}{\|}}{C}-\underset{\underset{\large H}{}}{N}-R^4$$

where W, Q, n, R^3 and R^4 have the above reported meaning, and their physiologically unobjectionable salts, with the qualification that X may signify tert-butoxy only when Y stands for the group

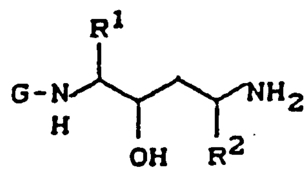
$$-\overset{\overset{\large Q}{\|}}{C}-NH-R^4 \quad \text{or}$$

characterized by the fact that compounds of general formula (II)



(II)

in which R^1 and R^2 have the above-given meaning, G stands for one of the above-listed amino protective groups and V stands for a radical capable of being split off hydrogenolytically, e.g. benzyl, are first reduced by hydrogenolysis with opening of the isoxazolidine ring into the amino alcohols of general formula (III)



(III)

where G, Z, R^1 and R^2 have the above-reported meaning, and then possibly condensed with compounds of general formula (IV) or (IVa)

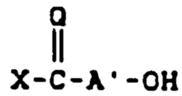
HO—L'—M'—Y (IV) HO-Y (IVa)

in which Y has the above-given meaning, and L' and M' have the above given meaning for L and M but not simultaneously standing for a direct bond, in inert solvents, if necessary in the presence of a water-removing accessory material and/or a base, and then after splitting off of protective G by conventional methods are reacted with compounds of general formula (V)

G'—B'—D'—OH (V)

in B' and D' have the above-given meanings of B and D but do not stand simultaneously for a direct bond, and G' has the above given meaning for G and

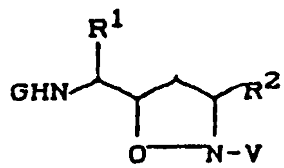
is the same as or different from it, and in a last step after the splitting off of the protective group G', are reacted with compounds of formula (VI)



(VI)

in which X and Q have the above given meaning, and A' has the meaning given above for A but does not stand for a direct bond, if necessary in the presence of a base.

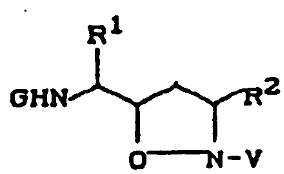
6. Compounds of general formula (II)



(II)

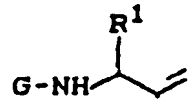
in which R^1 and R^2 are the same or different and stand for straight chained or branched alkyl with up to 8 carbon atoms which may possibly be substituted by cycloalkyl with 3 to 8 carbon atoms or by aryl with 6 to 10 carbon atoms, G for an amino protective group, and V for a radical that can be split off hydrogenolytically, e.g. benzyl.

7. Process for synthesis of compounds of general formula (II)



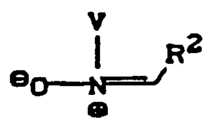
(II)

in which R^1 and R^2 have the above reported meaning, G stands for one of the above mentioned amino protective groups, and V for a radical that can be split off hydrogenolytically, e.g. benzyl, characterized by the fact that compounds of general formula (VII)



(VII)

in which G has the above given meaning, are reacted in a cycloaddition reaction with compounds of general formula (VIII)



(VIII)

in which V and R^2 have the above given meanings, if necessary in the presence of inert organic solvents.

8. Drugs containing at least one compound of general formula (I) as per claim 1.

9. Process for producing drugs [pharmaceutical preparations] characterized by the fact that at least one compound of general formula (I) as per claim 1 is transformed into a suitable application form, if necessary by using conventional accessory materials and vehicles.

10. Use of compounds of general formula (I) as in claim 1 in producing pharmaceutical preparations with a renin inhibitory action.